A. Harris 305084

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E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      2      CANCELLOUS BONE/CT
E2           0      1      CANCELLUS/CT
E3        7033      2 --> CANCER/CT
E4           0      2      CANCER (DISEASE)/CT
E5           3     26      CANCER (GENUS)/CT

=> e e3+all/ct
E1        7033    -->  Cancer/CT
                    HN   Valid heading during volumes 66-95 (1967-1981) only.
E2       66756     NEW  Neoplasm/CT
*********  END***

=> e endothelin b receptor/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      2      ENDOTHELIN 3 RECEPTORS/CT
E2           0      2      ENDOTHELIN A RECEPTORS/CT
E3           0        --> ENDOTHELIN B RECEPTOR/CT
E4           0      2      ENDOTHELIN B RECEPTORS/CT
E5           0      2      ENDOTHELIN B1 RECEPTORS/CT

=> e e4+all/ct
E1           0    -->  Endothelin b receptors/CT
E2                  USE  Endothelin receptors (L) ETB/CT
*********  END***

=> e melanoma/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      1      MELANOLEUCUS/CT
E2           1             MELANOLOPHIA/CT
E3        8270     16 --> MELANOMA/CT
E4           0      5      MELANOMA (L) AMELANOTIC/CT
E5           0      2      MELANOMA (L) EYE/CT

=> e e3+all/ct
E1        4323    BT2  Disease, animal/CT
E2       66756      BT1  Neoplasm/CT
E3        8270        -->  Melanoma/CT
                         HN   Valid heading during volume 66 (1967) to present.
                         NOTE For melanomas of specific anatomical parts, see
                              the specific anatomical part heading
E4                       OLD  Skin (L) melanoma/CT
E5                       UF   Malignant melanoma/CT
E6                       UF   Melanocarcinoma/CT
E7                       UF   Melanocytic tumor/CT
E8                       UF   Melanoma, malignant/CT
E9                       UF   Melanotic tumor/CT
E10                      UF   Neoplasm (L) melanoma/CT
E11                      UF   Skin, neoplasm (L) melanoma/CT
E12        328           NT1  Melanoma metastasis/CT
E13       4461           RT   Melanins/CT
E14       2020           RT   Melanocyte/CT
E15        138           RT   Melanoma growth-stimulating activity-.alpha./CT
E16       4546           RT   Skin, neoplasm/CT
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*********  END***

=> s e2-e16
          66756 NEOPLASM/CT
           8270 MELANOMA/CT
          58525 SKIN/CT
          12306 MELANOMA/IT
            309 MELANOMAS/IT
          12312 MELANOMA/IT
                  ((MELANOMA OR MELANOMAS)/IT)
            230 "SKIN (L) MELANOMA"/CT
              0 "MALIGNANT MELANOMA"/CT
              0 MELANOCARCINOMA/CT
              0 "MELANOCYTIC TUMOR"/CT
              0 "MELANOMA, MALIGNANT"/CT
              0 "MELANOTIC TUMOR"/CT
          66756 NEOPLASM/CT
          12306 MELANOMA/IT
            309 MELANOMAS/IT
          12312 MELANOMA/IT
                  ((MELANOMA OR MELANOMAS)/IT)
            124 "NEOPLASM (L) MELANOMA"/CT
           4546 SKIN, NEOPLASM/CT
          12306 MELANOMA/IT
            309 MELANOMAS/IT
          12312 MELANOMA/IT
                  ((MELANOMA OR MELANOMAS)/IT)
             94 "SKIN, NEOPLASM (L) MELANOMA"/CT
            328 "MELANOMA METASTASIS"/CT
           4461 MELANINS/CT
           2020 MELANOCYTE/CT
            138 "MELANOMA GROWTH-STIMULATING ACTIVITY-.ALPHA."/CT
           4546 "SKIN, NEOPLASM"/CT
L1        82455 (NEOPLASM/CT OR MELANOMA/CT OR "SKIN (L) MELANOMA"/CT OR "MALIGN
                ANT MELANOMA"/CT OR MELANOCARCINOMA/CT OR "MELANOCYTIC TUMOR"/CT
                 OR "MELANOMA, MALIGNANT"/CT OR "MELANOTIC TUMOR"/CT OR "NEOPLAS
                M (L) MELANOMA"/CT OR "SKIN, NEOPLASM (L) MELANOMA"/CT OR "MELAN
                OMA METASTASIS"/CT OR MELANINS/CT OR MELANOCYTE/CT OR "MELANOMA
                GROWTH-STIMULATING ACTIVITY-.ALPHA."/CT OR "SKIN, NEOPLASM"/CT)

=> e prostate cancer/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      2      PROSTATE BENIGN HYPERPLASIA/CT
E2           0      2      PROSTATE BENIGN HYPERTROPHY/CT
E3           0      2 --> PROSTATE CANCER/CT
E4           0      3      PROSTATE CANCER INHIBITORS/CT
E5           0      2      PROSTATE CANCER METASTASIS/CT

=> e e3+all/ct
E1           0    -->  Prostate cancer/CT
E2                  USE  Prostate gland (L) neoplasm/CT
*********  END***

=> e colon cancer/ct 5
E#   FREQUENCY     AT      TERM
--   ---------     --      ----
E1           0      3      COLON ADENOCARCINOMA METASTASIS INHIBITORS/CT
E2           0      2      COLON BACTERIA/CT
E3           0      2 --> COLON CANCER/CT
E4           0      3      COLON CANCER INHIBITORS/CT
E5           0      3      COLON CANCER INHIBITORS (L) COLORECTAL/CT

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```
=> e e3+all/ct
E1            0   -->  Colon cancer/CT
E2                   USE  Intestine, neoplasm (L) colon/CT
*********  END***

=> e ovarian cancer/ct 5
E#   FREQUENCY    AT     TERM
--   ---------    --     ----
E1           0     3     OVARIAN ADENOCARCINOMA INHIBITORS/CT
E2           0     2     OVARIAN ANTRAL FOLLICLE/CT
E3           0     2 --> OVARIAN CANCER/CT
E4           0     3     OVARIAN CANCER INHIBITORS/CT
E5           0     3     OVARIAN CANCER METASTASIS INHIBITORS/CT

=> e e3+all/ct
E1            0   -->  Ovarian cancer/CT
E2         5411     USE  Ovary, neoplasm/CT
*********  END***

=> e mammary cancer/ct 5
E#   FREQUENCY    AT     TERM
--   ---------    --     ----
E1           0     2     MAMMARY ADENOCARCINOMA/CT
E2           0     2     MAMMARY ADENOCARCINOMA METASTASIS/CT
E3           0     2 --> MAMMARY CANCER/CT
E4           0     3     MAMMARY CANCER INHIBITORS/CT
E5           0     2     MAMMARY CANCER METASTASIS/CT

=> e e3+all/ct
E1            0   -->  Mammary cancer/CT
E2                   USE  Mammary gland (L) neoplasm/CT
*********  END***

=> fil medl,biosis,biotechno,caplus,embase,jicst,wpids
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               29.93     117.78

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                0.00      -1.76

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=> s (cancer or neoplasm or melanoma or l1 or prostate cancer or colon cancer or
ovar? cancer or mammary cancer or ovary(a)neoplasm or mammary(1w)gland(l)neoplasm
or prostate (1w)gland(l)neoplasm or intestin?(1w)neoplasm(l)colon)
L2      1188530 FILE MEDLINE
L3       466819 FILE BIOSIS
L4       103937 FILE BIOTECHNO
L5       320438 FILE CAPLUS
L6       641274 FILE EMBASE
L7       136008 FILE JICST-EPLUS
L8        32969 FILE WPIDS

TOTAL FOR ALL FILES
L9      2889975 (CANCER OR NEOPLASM OR MELANOMA OR L1 OR PROSTATE CANCER OR
                COLON CANCER OR OVAR? CANCER OR MAMMARY CANCER OR OVARY(A) NEOPL
                ASM OR MAMMARY(1W) GLAND(L) NEOPLASM OR PROSTATE (1W) GLAND(L)
                NEOPLASM OR INTESTIN?(1W) NEOPLASM(L) COLON)

=> s (endothelin receptor(l)etb or endothelin receptor!) and l9
L10          23 FILE MEDLINE
L11          19 FILE BIOSIS
L12           4 FILE BIOTECHNO
L13         103 FILE CAPLUS
L14           8 FILE EMBASE
L15           2 FILE JICST-EPLUS
L16           6 FILE WPIDS

TOTAL FOR ALL FILES
L17         165 (ENDOTHELIN RECEPTOR(L) ETB OR ENDOTHELIN RECEPTOR!) AND L9

=> s l17 and endothelin 1
L18          17 FILE MEDLINE
L19          15 FILE BIOSIS
L20           4 FILE BIOTECHNO
L21          63 FILE CAPLUS
L22           7 FILE EMBASE
L23           2 FILE JICST-EPLUS
L24           0 FILE WPIDS

TOTAL FOR ALL FILES
L25         108 L17 AND ENDOTHELIN 1

=> s l25 and (treat? or therap?)
L26           1 FILE MEDLINE
L27           1 FILE BIOSIS
L28           1 FILE BIOTECHNO
L29          20 FILE CAPLUS
L30           1 FILE EMBASE
L31           0 FILE JICST-EPLUS
L32           0 FILE WPIDS

TOTAL FOR ALL FILES
L33          24 L25 AND (TREAT? OR THERAP?)

=> dup rem l33
PROCESSING COMPLETED FOR L33
L34          21 DUP REM L33 (3 DUPLICATES REMOVED)

=> d cbib abs 1-21;s l17 and e cadherin


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L34 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2001 ACS

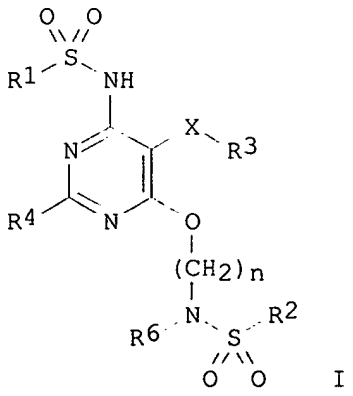
2001:320060 Document No. 134:339179 Nucleic acids and proteins associated with **cancer** as antitumor targets. Burmer, Glenna C.; Brown, Joseph P.; Pritchard, David (Lifespan Biosciences, Inc., USA). PCT Int. Appl. WO 2001030964 A2 20010503, 98 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US29126 20001020. PRIORITY: US 1999-PV161232 19991022.

AB This invention relates to the discovery of nucleic acids assocd. with cell proliferation, neoplasia, cell transformation, malignant tumor formation and metastasis and uses therefor. The present invention provides a method for **cancer** diagnosing by detecting the overexpression or the underexpression of a **cancer**-assocd. mRNA in the tissue of interest, preferably in liver, breast, prostate, kidney and colon. In another aspect, the invention provides methods for arresting **cancer** and a method for identifying a modulators of **cancer** development.

L34 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2001 ACS

2001:185734 Document No. 134:237487 Preparation of pyrimidine bis-sulfonamides as endothelin antagonists. Bolli, Martin; Boss, Christoph; Clozel, Martine; Fischli, Walter (Actelion Pharmaceuticals Ltd, Switz.). PCT Int. Appl. WO 2001017976 A1 20010315, 92 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-EP7999 20000816. PRIORITY: WO 1999-EP6485 19990903; WO 2000-EP1222 20000215.

GI



I

AB 4-(Sulfonylamino)-6-(sulfonylaminoalkoxy)pyrimidine derivs. [I; R1 represents aryl, aryl-lower alkyl, aryl-lower alkenyl, heteroaryl, heteroaryl-lower alkyl; R2 represents lower alkyl, trifluoromethyl, lower alkoxy-lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl-lower alkyl,

aryl-lower alkenyl, heterocyclyl, heterocyclyl-lower alkyl, heteroaryl, etc.; R3 represents (un)substituted Ph, benzofuranyl, aryl, heteroaryl; R4 represents hydrogen, halogen, trifluoromethyl, lower alkyl, lower alkylamino, lower alkyloxy, lower alkylsulfono, lower alkylsulfinyl, lower alkylthio, lower alkylthio-lower alkyl, hydroxy-lower alkyl, lower alkyloxy-lower alkyl, hydroxy-lower alkyloxy-lower alkyl, hydroxy-lower alkylamino, lower alkylamino-lower alkyl, amino, etc.; R6 represents hydrogen, lower alkyl, cycloalkyl, heterocyclyl, heteroaryl, aryl, cycloalkyl-lower alkyl, heterocyclyl-lower alkyl, heteroaryl-lower alkyl, aryl-lower alkyl, lower alkoxy-lower alkyl, lower alkylthio-lower alkyl, etc.; n represents the nos. 2,3,4 and 5; X represents oxygen, sulfur, NH, CH2, or a bond] and pure diastereomers, mixts. of diastereomers, diastereomeric racemates, mixts. of diastereomeric racemates and the meso-forms and pharmaceutically acceptable salts thereof are prepd. Because of their ability to inhibit the endothelin binding, the described compds. can be used for **treatment** of diseases which are assocd. with an increase in vasoconstriction, proliferation or inflammation due to endothelin. Examples of such diseases are hypertension, coronary diseases, myocardial insufficiency, renal and myocardial ischemia, renal failure, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, Raynaud's syndrome, portal hypertension and pulmonary hypertension. They can also be used for atherosclerosis, prevention of restenosis after balloon or stent angioplasty, inflammation, stomach and duodenal ulcer, **cancer**, prostatic hypertrophy, erectile dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram neg. septicemia, shock, sickle cell anemia, glomerulonephritis, renal colic, glaucoma, **therapy** and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin **treatment**, as well as other diseases presently known to be related to endothelin. Thus, 4-tert-butyl-N-[6-(3-aminopropoxy)-5-(o-methoxyphenoxy)-2-cyclopropyl-4-pyrimidinyl]benzenesulfonamide was reacted with thiophene-2-sulfonyl chloride in dry dichloromethane and dry DMF in the presence of Hunig's base at room temp. for 12 h to give 4-tert-butyl-N-[6-[3-(thiophene-2-sulfonylamino)propoxy]-5-(o-methoxyphenoxy)-2-cyclopropyl-4-pyrimidinyl]benzenesulfonamide (II). II inhibited the binding of [125I]**endothelin-1** to microsomal membranes from recombinant CHO cells expressing recombinant EtA or EtB receptor with IC50 of 14.8 and 1.86 nM for EtA and EtB receptor, resp.

L34 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2001 ACS

2001:396348 Document No. 135:102620 The role of small bioactive peptides and cell surface peptidases in androgen independent **prostate cancer**. Nelson, Joel B. (Brady Urol. Inst., Johns Hopkins Med. Inst., Baltimore, MD, USA). Prostate Cancer, 433-447. Editor(s): Chung, Leland W. K.; Isaacs, William B.; Simons, Jonathan W. Humana Press Inc.: Totowa, N. J. (English) 2001. CODEN: 69BIZN.

AB A review with 120 refs. At current rates of diagnosis, a man in the United States has a one-in-five chance that invasive **prostate cancer** will develop in his lifetime. This rate is nearly twice that of lung **cancer** and three times that of colorectal **cancer**. Death from **prostate cancer** is the second leading cause of death from **cancer** in men in the United States. Almost every man with advanced **prostate cancer** will undergo androgen ablation **therapy** and in time, most will progress. The central characteristic of fatal **prostate cancer** is androgen independence. These facts were established in 1941, when **therapeutic** castration was first described, and, unfortunately, still hold true as the 1990s drew to a close. Historically, there has been an inverse relationship between efforts to maximize the efficacy of hormonal **therapy** for **prostate cancer** and the outcomes of those efforts: thousands of patients

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studied and billions of dollars spent repeatedly show hormonal **therapy** to have dramatic-yet ultimately ineffective-**therapeutic** effects. Although a no. of growth and survival factors have been implicated in the androgen independent phenotype of **prostate cancer**, there has been no translation of these findings to effective **therapy**. This review is not confined to the classic neuroendocrine phenotype (which, in its small cell or carcinoid manifestations represents a fraction of **prostate cancers**)-it examines a recent series of related observations about the role of the small bioactive peptides bombesin, **endothelin-1** (ET-1), and neurotensin in **prostate cancer**. These peptides-which have compelling biol. effects in **prostate cancer**-act through specific, high-affinity heptahelical, G-protein-coupled receptors. Collectively, recent observations may provide a broader understanding of androgen independent **prostate cancer**. Excitement for targeting these pathways in **therapy** has been fueled by early clin. trial results: the use of an endothelin-receptor antagonist has resulted in both objective and subjective responses.

L34 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2001 ACS
2000:790734 Document No. 133:329575 **Cancer treatment** with endothelin receptor antagonists. Schneider, Robert J.; Jamal, Sumayah (New York University, USA). PCT Int. Appl. WO 2000067024 A1 20001109, 64 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US11990 20000503. PRIORITY: US 1999-305084 19990504.

AB The present invention relates to **therapeutic** protocols and pharmaceutical compns. designed to **treat** and prevent **cancer**. More specifically, the present invention relates to a novel method of **treating cancer** using antagonists to the endothelin B receptor (ETB) or inactive mimic forms of **endothelin-1**. The pharmaceutical compns. of the invention are capable of selectively inhibiting the early events assocd. with the development of **cancer**. The present invention further relates to screening assays to identify compds. which inhibit ETB activation.

L34 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2001 ACS
2000:402104 Document No. 133:28258 Methods for detection of antiestrogen-resistant breast **cancer** by determining angiogenic factors and receptors. Fuqua, Suzanne A. W.; Friedrichs, William; Osborne, C. Kent; Hilsenbeck, Sue; Schiff, Rachel (Board of Regents, the University of Texas System, USA). PCT Int. Appl. WO 2000034788 A1 20000615, 104 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US28206 19991129. PRIORITY: US 1998-PV111428 19981208.

AB Disclosed are methods for the detection, diagnosis and prediction of tamoxifen-resistant breast **cancer**. Genetic and antibody probes and methods useful in detg. the presence and monitoring the progression of

breast **cancer** are also described. The methods involve detg. polypeptide or mRNA expression of the genes encoding the angiogenic agents or receptors TIE-2, EDNRA, TGF.beta.3, TGFR.beta.III, VEGFR1, VEGF or bFGFR. Also described are procedures for combination **therapies** utilizing antiangiogenic agents or gene **therapy** directed towards TIE-2, EDNRA, TGF.beta.3, TGFR.beta.III, VEGFR1, VEGF or bFGFR, in combination with tamoxifen **treatment** of breast **cancer**.

L34 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2001 ACS
2000:259979 Document No. 132:288794 Sympathetic nervous system activity-reducing agents for **treatment** of disease- or age-related weight loss and for enhancement of exercise performance. Anker, Stefan Dietmar; Coats, Andrew Justin Stewart (Imperial College Innovations Limited, UK). PCT Int. Appl. WO 2000021509 A2 20000420, 72 pp. DESIGNATED STATES: W: JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB3302 19991015. PRIORITY: GB 1998-22458 19981015; GB 1998-22459 19981015; GB 1999-17181 19990723.

AB A method of **treating** wt. loss due to underlying disease in a patient, the method comprising administering to the patient an effective amt. of an agent which reduces sympathetic nervous system activity. A method of **treating** wt. loss due to underlying disease in a patient, the method comprising administering to the patient an effective amt. of any one or more of the following: a compd. which inhibits the effect of aldosterone such as an aldosterone antagonist; a chymase inhibitor; a cathepsin B inhibitor; a .beta. receptor blocker; an imidazoline receptor antagonist; a centrally acting .alpha. receptor antagonist; a peripherally acting .alpha. receptor antagonist; a ganglion blocking agent; a drug that has an effect on cardiovascular reflexes and thereby reduces SNS activity such as an opiate; scopolamine; an endothelin receptor antagonist; and a xanthine oxidase inhibitor. The methods are particularly useful in **treating** cardiac cachexia. The sympathetic nervous system activity-reducing agents may also be used to **treat** wt. loss due to aging and to enhance exercise performance.

L34 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2001 ACS
2000:133697 Document No. 132:203144 Low-adenosine antisense oligonucleotide agents, compositions, kits and **treatments** for respiratory disorders. Nyce, Jonathan W. (East Carolina University, USA). PCT Int. Appl. WO 2000009525 A2 20000224, 1343 pp. DESIGNATED STATES: W: AU, CA, CN, MX, RU, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US17712 19990803. PRIORITY: US 1998-95212 19980803.

AB A compn. comprises a nucleic acid comprising an oligo antisense to a target such as polypeptide(s) assocd. with an ailment afflicting lung airways, genes and mRNAs encoding them, genomic and mRNA flanking regions, intron and exon borders and all regulatory and functionally related segments of the genes and mRNAs encoding the polypeptides, their salts and mixts. Various formulations contain a requisite carrier, and optionally other additives and biol. active agents. The agent of the invention may be prepd. by selecting a target gene(s), genomic flanking region(s), RNA(s) and/or polypeptide(s) assocd. with a disease(s) or condition(s) afflicting lung airways, obtaining the sequence of the mRNA(s) corresponding to the target gene(s) and/or genomic flanking region(s), and/or RNAs encoding the target polypeptide(s), selecting at least one segment of the mRNA which may be up to 60% free of thymidine (T) and synthesizing one or more antisense oligonucleotide(s) to the mRNA segments which are free of adenosine (A) by substituting a universal base for A when present in the oligonucleotide. The agent may be prepd. by selection of target nucleic acid sequences with GC running stretches, which have low T content, and by optionally replacing A in the antisense oligonucleotides with a universal base. The agent, compn. and formulations are used for

prophylactic, preventive and **therapeutic treatment** of ailments assocd. with impaired respiration, allergy(ies) and/or inflammation, such as pulmonary vasoconstriction, inflammation, allergies, asthma, impeded respiration, lung pain, cystic fibrosis, bronchoconstriction, pulmonary hypertension and bronchoconstriction, chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), ischemic conditions including ischemia itself, and **cancers** such as leukemias, lymphomas, carcinomas, and the like, e.g. **colon cancer**, breast **cancer**, pancreatic **cancer**, lung **cancer**, hepatocellular carcinoma, kidney **cancer**, **melanoma**, hepatic metastasis, etc., as well as all types of **cancers** with may metastasize or have metastasized to the lung(s), including breast and **prostate cancer**. The present **treatment** is suitable for administration in combination with other **treatments**, e.g. before, during and after other **treatments**, including radiation, chemotherapy, antibody **therapy** and surgery, among others. The present agent is effectively administered preventatively, prophylactically or **therapeutically** by itself for conditions without known **therapies**, or as a substitute for, or in conjunction with, other **therapies** exhibiting undesirable side effects. The **treatment** of this invention may be administered directly into the respiratory system of a subject, so that the agent has direct access to the airways and the lungs. The invention is exemplified with specificity and pharmacokinetic studies using phosphorothioated antisense oligonucleotides targeted to the adenosine receptors A1, A2a, A2b, and A3.

L34 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2001 ACS

2000:787984 Document No. 134:13680 Intracellular signaling mechanisms leading to synergistic effects of **endothelin-1** and stem cell factor on proliferation of cultured human melanocytes. Cross-talk via trans-activation of the tyrosine kinase c-kit receptor. Imokawa, Genji; Kobayasi, Takeshi; Miyagishi, Makoto (Kao Biological Science Laboratories, Tochigi, 321-3497, Japan). J. Biol. Chem., 275(43), 33321-33328 (English) 2000. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB The authors previously reported that activation of mitogen-activated protein kinase (MAPK) is involved in the mitogenic stimulation of normal human melanocytes (NHMC) by **endothelin-1** (ET-1). In the present study, the authors detd. signaling mechanisms upstream of MAPK activation that are involved in ET-1 stimulation and their synergism with stem cell factor (SCF). Pretreatment of cultured NHMC with ETB receptor antagonists, pertussis toxin, a specific phospholipase C inhibitor (U73122), or a protein kinase C inhibitor (calphostine) blocked a transient tyrosine phosphorylation of MAPK induced by ET-1, whereas the addn. of a calcium chelator (BAPTA) failed to inhibit that tyrosine phosphorylation of MAPK. **Treatment** with ET-1 and SCF together synergistically increased DNA synthesis, which was accompanied by synergism for MAPK phosphorylation. The time course of inositol 1,4,5-trisphosphate formation revealed that there is no difference in the level of inositol 1,4,5-trisphosphate stimulated by ET-1 + SCF or by ET-1 alone. Evaluations of the serine phosphorylation of MEK and Raf-1 activity showed a synergistic effect in SCF + ET-1-**treated** NHMC. Stimulation with SCF + ET-1 induced a more rapid and stronger tyrosyl phosphorylation of proteins corresponding to p52 and p66 Shc than did stimulation with SCF only, and this was accompanied by a stronger assocn. of tyrosine-phosphorylated Shc with Grb2. Interestingly, a more rapid and marked tyrosine phosphorylation of c-kit was also detected in NHMC-**treated** with SCF + ET-1 than NHMC **treated** with SCF only. These data indicate that the synergistic cross-talk between SCF and ET-1 signaling is initiated through the pathway of tyrosine phosphorylation of

c-kit, which results in the enhanced formation of the Shc-Grb2 complex which leads in turn to the synergistic activation of the Ras/Raf-1/MEK/MAP kinase loop.

L34 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2001 ACS
2001:126358 Document No. 134:305074 Expression of **endothelin 1** and endothelin a receptor in HPV-associated cervical carcinoma: new potential targets for anticancer **therapy**. Venuti, Aldo; Salani, Debora; Manni, Vanessa; Poggiali, Federica; Bagnato, Anna (Laboratories of Virology, Regina Elena Cancer Institute, Rome, 00158, Italy). FASEB J., 14(14), 2277-2283 (English) 2000. CODEN: FAJOEC. ISSN: 0892-6638. Publisher: Federation of American Societies for Experimental Biology.

AB Human papillomaviruses (HPV) are assocd. with cervical **cancer** and interact with growth factors that may enhance malignant transformation of cervical carcinoma cells. **Endothelin-1** (ET-1) is released from HPV-transfected keratinocytes and induces increased growth response in these cell lines in comparison with normal cells. In the present study several cervical carcinoma cell lines have been analyzed to investigate the expression of ET-1 and its receptors as well as their involvement in tumor growth. All HPV-pos. **cancer** cells secreted ET-1 and expressed mRNA for ET-1 and its receptors, whereas a HPV-neg. carcinoma cell line expressed only the ETBR mRNA and didn't secrete ET-1. Binding studies showed that HPV-assocd. cells expressed an increased no. of functional ETAR. ET-1 stimulated a marked dose-dependent increase in [3H]-thymidine incorporation with respect to the normal cells whereas ET-3 and ETBR agonists had no effect. In HPV-pos. **cancer** cells, a specific antagonist of ETAR inhibited the proliferation induced by ET-1 and substantially reduced the basal growth rate of unstimulated cervical tumor cells, whereas the ETBR antagonist had no effect. These results demonstrate that ET-1 participates in the progression of neoplastic growth in HPV-assocd. carcinoma, in which ETAR are increased and could be targeted for antitumor **therapy**.

L34 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2001 ACS
2001:14684 Document No. 134:145533 Modulation of human colon tumor-stromal interactions by the endothelin system. Egidy, Giorgia; Juillerat-Jeanneret, Lucienne; Jeannin, Jean-Francois; Korth, Petra; Bosman, Fred T.; Pinet, Florence (INSERM Unit 36, College of France, Paris, 75005, Fr.). Am. J. Pathol., 157(6), 1863-1874 (English) 2000. CODEN: AJPAA4. ISSN: 0002-9440. Publisher: American Society for Investigative Pathology.

AB Tumor neovascularization is considered to be a crit. step in the development of a malignant tumor. Endothelin (ET)-1 is a powerful vasoconstrictor and mitogenic peptide that is produced by many **cancer** cell lines. The cellular distribution of the ET components was evaluated in human colon tumors and compared to normal colon. There was more of the ET components (prepro-ET-1, endothelin-converting enzyme-1, and ETA and ETB receptors) in adenomas and adenocarcinomas than in the normal colon. There was overprodn. of preproET-1 and endothelin-converting enzyme-1 in carcinoma cells and stromal vessels, suggesting that they are a local source of ET-1. ETA receptors were present in stromal myofibroblasts of neoplastic tissue, and there were large amts. of ETB receptors in the endothelium and myofibroblasts. There was also a redistribution of .alpha.-smooth muscle actin-pos. cells in the vascular structures of tumors. An exptl. rat model of induced **colon cancer treated** for 30 days with bosentan, a mixed antagonist of both ET receptors, confirmed the morphol. changes obsd. during the tumor vascularization. Our data suggest that ET-1 and its receptor play a role in **colon cancer** progression, with ET-1 functioning as a neg. modulator of the stromal response.

Searched by: Mary Hale 308-4258 CM-1 12D16

L34 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2001 ACS
2000:671388 Document No. 134:129372 **Endothelin-1** stimulates aldosterone synthesis in Conn's adenomas via both A and B receptors coupled with the protein kinase C- and cyclooxygenase-dependent signaling pathways. Rossi, Gian Paolo; Andreis, Paola G.; Neri, Giuliano; Tortorella, Cinzia; Pelizzo, Maria Rosa; Sacchetto, Alfredo; Nussdorfer, Gastone G. (Departments of Clinical and Experimental Medicine School of Medicine, University of Padua, Padua, I-35121, Italy). J. Invest. Med., 48(5), 343-350 (English) 2000. CODEN: JINVFI. ISSN: 1081-5589. Publisher: Lippincott Williams & Wilkins.

AB The mechanisms and factors leading to enhanced aldosterone secretion and ultimately to neoplastic transformation of the adrenal cortex are poorly defined. Angiotensin-II (Ang-II) and **endothelin-1** (ET-1) have emerged as likely candidates among potential aldosterone secretagogues and adrenocortical growth-promoting factors. We therefore compared the effects of Ang-II and ET-1 on steroid hormone secretion of Conn's adenomas. Ten Conn's adenomas that showed responsiveness to Ang-II blockade in vivo were recruited. Fragments of the tumors were collected immediately after surgical excision, and dispersed cells were obtained by collagenase digestion and mech. disaggregation. Steroid hormones secreted by dispersed Conn's adenoma cells were assayed by quant. high-performance liq. chromatog. or RIA. Both Ang-II and ET-1 (10-9 mol/L) similarly enhanced the overall steroid hormone prodn. ET-1 raised the release of pregnenolone (as evaluated by blocking its further metab. by cyanoketone), corticosterone, 18-hydroxycorticosterone, and aldosterone, without affecting that of 11-deoxycortisol, cortisol, and 11-deoxycorticosterone. The hormonal responses to ET-1 were partially reversed by 10-7 mol/L of either the ETA-receptor antagonist BQ-123 or the ETB-receptor antagonist BQ-788 and were abolished when both antagonists were used together. The aldosterone response to the selective activation of ETA and ETB receptors was studied in three Conn's adenomas by exposing dispersed cells to ET-1 (10-9 mol/L) plus BQ-788 (10-7 mol/L) and to the ETB -receptor agonist BQ-3020 (10-8 mol/L). Both **treatments** raised aldosterone output by about 2-fold. ETA receptor-mediated aldosterone response was abolished by the protein kinase (PK) C inhibitor calphostin C (10-5 mol/L). ETB receptor-mediated secretory response was lowered by either calphostin C and the cyclooxygenase (COX) inhibitor indomethacin (10-5 or 10-4 mol/L) and was completely suppressed when these two were combined. The PKA inhibitor H-89 and the lipoxygenase inhibitor phenidone were ineffective. Collectively, our findings indicate that Ang-II and ET-1 equipotently stimulate both early and late steps of aldosterone synthesis in Conn's adenoma cells. The secretagogue effect of ET-1 occurs via the activation of ETA and ETB receptors, which are coupled with the PKC-dependent and the PKC- and COX-dependent signaling pathway, resp.

L34 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2001 ACS
2000:701382 Document No. 134:40274 Differential Regulation of Endothelin Secretion and Endothelin Receptor mRNA Levels in JAR, JEG-3, and BeWo Choriocarcinoma Cell Lines and in Human Trophoblasts, Their Nonmalignant Counterpart. Bilban, M.; Barth, S.; Cervar, M.; Mauschitz, R.; Schaur, R. J.; Zivkovic, F.; Desoye, G. (Department of Obstetrics and Gynecology, University of Graz, Graz, A-8036, Austria). Arch. Biochem. Biophys., 382(2), 245-252 (English) 2000. CODEN: ABBIA4. ISSN: 0003-9861. Publisher: Academic Press.

AB Endothelin (ET) secretion and expression of both ET-A and ET-B receptor subtypes have been found in a no. of primary **cancers**. The present study tested (1) whether choriocarcinoma cells and their nonmalignant counterpart, the trophoblast, secrete ET-1 and express ET-A and ET-B receptors; (2) whether ET-1 secretion and receptor mRNA levels are regulated by the same factors in nonvascular tissues as in vascular tissues; and (3) whether such regulation is similar in malignant and

nonmalignant cells. All cells secreted ET-1 in similar amts. (.apprx.0.8 fmol/106 cells per 24 h) and secretion was unaffected by culture and **treatment**. Whereas ET-B accounted for almost all (>98%) ET receptor transcripts in the choriocarcinoma cells, the trophoblasts expressed about 20% ET-A receptor mRNA. During control cultures, ET-B mRNA levels rose in choriocarcinoma, with the greatest relative increase (6-fold; vs. 0 h) in BeWo, whereas in trophoblasts, ET-A mRNA transiently changed after 24 and 48 h. **Treatment** with dexamethasone and glucose did not alter the mRNA levels in all cells. Insulin induced changes in ET-B mRNA levels in BeWo (+90 and +60% after 24 and 48 h, resp.) and JEG-3 (-70%), but not in JAR and trophoblast cells. The authors conclude that malignant transformation affects the responsiveness of the endothelin receptor system to external stimuli and that the regulation of the endothelin system differs in vascular and nonvascular tissues. (c) 2000 Academic Press.

L34 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2001 ACS
2000:549637 Document No. 133:261582 Endothelins in the urinary tract. Sullivan, M. E.; Mumtaz, F. H.; Khan, M. A.; Dashwood, M. R.; Thompson, C. S.; Mikhailidis, D. P.; Morgan, R. J. (Departments of Urology, Royal Free Hampstead NHS Trust, London, UK). BJU Int., 86(1), 97-106 (English) 2000. CODEN: BJINFO. ISSN: 1464-4096. Publisher: Blackwell Science Ltd..
AB A review, with 103 refs. The discovery in 1985 and isolation in 1988 of **endothelin-1** (ET-1) has generated considerable research. The studies within the urinary tract have shown that ETs can be formed by numerous cells as well as the endothelium. ET appears to function as a local rather than a circulating hormone. These autocrine and paracrine actions suggest that ET has the potential to regulate numerous functions within the urinary tract, either directly or indirectly, by interacting with neuroendocrine regulatory systems. Physiol., ET-1 produces potent, long-lasting contractions via the ETA receptor of all smooth muscles studied in the urinary tract. Further work is required in this area, although it clearly has potential for **therapeutic** targeting. Alterations in the no. and/or affinity of the ET receptor subtypes has been shown in numerous disease conditions. This appears to be particularly significant in renal cell carcinoma and prostate adenocarcinomas, where the loss or redn. of ETB receptor expression may be a common pathway in progression of the **cancer**. A better understanding of the distribution and regulation of function of ET receptor subtypes, the localization and isolation of endothelin-converting enzymes, and the physiol. and pathophysiol. significance of endogenously produced ETs is now needed to clarify the true roles of the ET peptide family in the urinary tract.

L34 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2001 ACS
2000:297203 Document No. 133:41224 The role of **endothelin-1** and endothelin receptor antagonists in **prostate cancer**. Nelson, J. B.; Carducci, M. A. (The James Buchanan Brady Urological Institute, The Johns Hopkins Oncology Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA). BJU Int., 85(Suppl. 2), 45-48 (English) 2000. CODEN: BJINFO. ISSN: 1464-4096. Publisher: Blackwell Science Ltd..
AB A review is given with 52 refs. on **endothelin-1** (ET-1) in **prostate cancer** including the topics ET-1 and its receptors, expression of ET-1 and its receptors in prostate cells and in **prostate cancer** cells, and the use of ET receptor antagonists in **prostate cancer**.

L34 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2001 ACS
1999:795994 Document No. 132:31744 Gene probes used for genetic profiling in healthcare screening and planning. Roberts, Gareth Wyn (Genostic Pharma Ltd., UK). PCT Int. Appl. WO 9964627 A2 19991216, 745 pp. DESIGNATED

Searched by: Mary Hale 308-4258 CM-1 12D16

STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1780 19990604. PRIORITY: GB 1998-12099 19980606; GB 1998-13291 19980620; GB 1998-13611 19980624; GB 1998-13835 19980627; GB 1998-14110 19980701; GB 1998-14580 19980707; GB 1998-15438 19980716; GB 1998-15576 19980718; GB 1998-15574 19980718; GB 1998-16085 19980724; GB 1998-16086 19980724; GB 1998-16921 19980805; GB 1998-17097 19980807; GB 1998-17200 19980808; GB 1998-17632 19980814; GB 1998-17943 19980819.

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, **therapy** and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic.RTM." profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L34 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2001 ACS

1999:795993 Document No. 132:31743 Gene probes used for genetic profiling in healthcare screening and planning. Roberts, Gareth Wyn (Genostic Pharma Limited, UK). PCT Int. Appl. WO 9964626 A2 19991216, 149 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1779 19990604. PRIORITY: GB 1998-12098 19980606; GB 1998-28289 19981223.

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, **therapy** and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a

technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

L34 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2001 ACS
1999:722912 Document No. 131:317804 Methods for **treatment** of pain by inhibiting **endothelin-1** action. Davar, Gudarz (USA). PCT Int. Appl. WO 9956761 A1 19991111, 39 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US9732 19990504. PRIORITY: US 1998-72428 19980504.
AB A method of detg. whether a compd. alleviates nerve pain mediated by **endothelin-1** (ET-1) involves (i) detg. whether the compd. has the ability to inhibit a ET-1 action and then (ii) detg. whether the compd. reduces nerve pain by testing the compd. in human patients suffering from pain mediated by the ET-1 action. The invention also includes a method of detg. whether a compd. alleviates pain caused by nerve injury in human patients by detg. the compd. ability to inhibit an inflammatory leukocyte response. ET-1 (40-800 .mu.M) applied to rat sciatic nerve in vivo induced direct effect on sensory neurons and pain behavior via a mechanism independent of vasoconstriction of sciatic nerve microvessels. ET-1-induced pain behavior is mediated by ATA subtype of receptor on neurons, as evidenced by using ETA and ETB receptor antagonists, BQ-123 and BQ-788, resp. Therefore, the inhibition of ET-1's vasoconstriction-independent mechanism of causing pain is an effective pain **treatment**, esp. under conditions where ET-1 levels are elevated in a patient, such as metastatic **prostate cancer**. Furthermore, given that ET-1 acts directly on the sensory neuron ETA receptor, the ETA receptor is an important **therapeutic** target.

L34 ANSWER 18 OF 21 BIOSIS COPYRIGHT 2001 BIOSIS
1999:47505 Document No.: PREV199900047505. Endothelins as autocrine regulators of tumor cell growth. Bagnato, Anna (1); Catt, Kevin J.. (1) Lab. Molecular Pathol. Ultrastructure, Regina Elena Cancer Inst., Via delle Messi D'Oro 156-158, 00158 Rome Italy. Trends in Endocrinology and Metabolism, (Nov., 1998) Vol. 9, No. 9, pp. 378-383. ISSN: 1043-2760. Language: English.
AB **Endothelin 1** (ET-1) is produced by several types of human **cancer** cells and has been proposed to participate in tumor development or progression by exerting autocrine or paracrine actions on neoplastic cells and their surrounding stromal cells. Recently, an ET-1-mediated autocrine loop has been implicated in the growth of ovarian tumor cells. The co-expression of ET-1 and ETA receptors, with consequent activation of growth signaling pathways in human ovarian carcinoma cells, constitutes a mechanism for the autocrine regulation of tumor cell growth. Such findings also provide a basis for further investigation of the role of tyrosine phosphorylation in ET-1-regulated growth responses in ovarian tumor cells. The overexpression of ET-1 and its receptor in **cancer** cells may serve as a tumor marker, and could provide potential targets for **therapy**.

L34 ANSWER 19 OF 21 MEDLINE DUPLICATE 1
97141778 Document Number: 97141778. PubMed ID: 8988036. Methylation of the 5' CpG island of the endothelin B receptor gene is common in human

prostate cancer. Nelson J B; Lee W H; Nguyen S H; Jarrard D F; Brooks J D; Magnuson S R; Opgenorth T J; Nelson W G; Bova G S. (James Buchanan Brady Urological Institute Research Laboratories, Johns Hopkins Hospital, Baltimore, Maryland 21287-2411, USA.) CANCER RESEARCH, (1997 Jan 1) 57 (1) 35-7. Journal code: CNF; 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Production of the potent vasoconstrictor **endothelin-1** (ET-1) by human **prostate cancer** cells accompanies **prostate cancer** progression in vivo. The predominant **endothelin receptor** expressed by normal prostate epithelium, **ETB**, is not expressed by any of the established human **prostate cancer** cell lines, and **ETB** binding is decreased on **prostate cancer** tissues. **ETB**, which may mediate ET-1 clearance and may inhibit ET-1 secretion, is encoded by a gene that contains a 5' CpG island encompassing the transcriptional regulatory region. We examined this regulatory region of the **ETB** receptor gene (EDNRB) to determine whether hypermethylation of cytidine nucleotides accompanies decreased **ETB** expression in human **prostate cancer**. We found somatic methylation of CpG island sequences in EDNRB in 5 of 5 human **prostate cancer** cell lines, 15 of 21 primary **prostate cancer** tissues, and 8 of 14 **prostate cancer** metastases (70% of samples overall). Normal tissues contained only unmethylated EDNRB. **Treatment** of human prostatic carcinoma cell line cultures with 5-azacytidine induced **ETB** mRNA expression, suggesting that CpG island methylation changes might accompany the apparent transcriptional silencing of EDNRB in vivo.

L34 ANSWER 20 OF 21 BIOTECHNO COPYRIGHT 2001 Elsevier Science B.V.DUPLICATE

AN 1995:25070021 BIOTECHNO

AB Endothelins (ETs) (ET-1, ET-2, and ET-3), a family of 21-amino acid peptides, mediate a host of biological responses by binding to specific cell surface receptors termed ET(A) and ET(B). Because a role for ET in bone remodeling has been suggested, the present study was undertaken (a) to characterize ET receptors and their responses in the rat osteosarcoma cell line ROS 17/2.8 and (b) to study their regulation by 1,25-dihydroxyvitamin D.sub.3. Binding studies using .sup.1.sup.2.sup.5I-ET-1 (a nonselective agonist) and .sup.1.sup.2.sup.5I- IRL-1620 (an ET(B) receptor-selective agonist) indicated that these sells display high affinity ET(A) and ET(B) receptors in the ratio of 3:1. Addition of ET-1 or sarafotoxin 6c to myo-.cents..sup.3H!inositol-labeled cells resulted in an increase in inositol phosphate accumulation as well as in intracellular Ca.sup.2.sup.+ release, suggesting that these receptors are coupled to phospholipase C. In addition, ET-1 but not sarafotoxin 6c induced a modest increase in the expression of osteocalcin protein that was completely blocked by BQ123 (an ET(A) receptor-selective antagonist), indicating that activation of ET(A) receptors plays a role in the induction of osteocalcin. **Treatment** of ROS osteoblasts with 10 nM 1,25-dihydroxy-vitamin D.sub.3 for 14 hr resulted in a significant (>50%) decrease in .sup.1.sup.2.sup.5I-ET-1 and .sup.1.sup.2.sup.5I-IRL-1620 binding. This decrease in binding was shown to be due to a decrease in the number of ET receptors, with no change in affinity. Although both ET(A) and ET(B) receptors were down-regulated in response to 1,25-dihydroxy-vitamin D.sub.3, only ET(A) receptor mRNA levels were significantly decreased, with very little change in ETa mRNA levels. These data indicate that ROS osteoblasts display both ET(A) end ET(B) receptors that are functional. Induction of osteocalcin was primarily mediated by ET(A) receptors, and these receptors were also down-regulated at the mRNA level by 1,25-dihydroxy-vitamin D.sub.3.

L34 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2001 ACS

1995:211010 Document No. 122:475 A selective endothelin ETA antagonist,

Searched by: Mary Hale 308-4258 CM-1 12D16

BQ-123, inhibits 125I-**endothelin-1** (125I-ET-1) binding to human meningiomas and antagonizes ET-1-induced proliferation of meningioma cells. Kitagawa, Naoki; Tsutsumi, Keisuke; Niwa, Masami; Yamaga, Sei-ichi; Anda, Takeo; Khalid, Humayun; Himeno, Akihiko; Taniyama, Kohtaro; Shibata, Shobu (Department Neurosurgery, Nagasaki University School Medicine, Nagasaki, 852, Japan). Cell. Mol. Neurobiol., 14(2), 105-18 (English) 1994. CODEN: CMNEDI. ISSN: 0272-4340.

AB The authors studied the effects of BQ-123, a selective ETA receptor antagonist, on 125I-**endothelin-1** (125I-ET-1) binding to cell surface receptors in surgically excised human meningiomas and on ET-1-induced DNA synthesis in cultured human meningioma cells in vitro, using a quant. receptor autoradiog. technique with radioluminog. and 3H-thymidine incorporation, resp. All of the human meningiomas expressed high-affinity binding sites for 125I-ET-1, regardless of differences in histol. subtypes (Kd=2.6 nM, Bmax = 374 fmol/mg). BQ-123 competed for 125I-ET-1 binding to sections of meningiomas with IC50s of 3.2.times.10-7 M, and 10-4 M BQ-123 displaced 80% of the binding. ET-1 significantly stimulated DNA synthesis in cultured human meningioma cells, up to 170% of the basal level in the presence of 10-9 M ET-1. BQ-123 inhibited ET-1 (10-9 M)-induced DNA synthesis in meningioma cells, in a dose-dependent manner, and 10-5 M BQ-123 reduced it to 120% of the basal level. The no. of meningioma cells detd. after 4 days in culture was dose dependently increased in the presence of ET-1 (10-9 and 10-7 M). The growth rate of meningioma cells, incubated with 10-9 M ET-1, was reduced by 50% in the presence of 10-7 M BQ-123. The authors' data suggest that (a) human meningioma cells express a large no. of ETA **endothelin receptors**, with a small proportion of non-ETA receptors linked to proliferation of the cells, and (b) ET receptor antagonists, including BQ-123, might prove to be effective **treatment** for patients with meningioma.

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L35           0 FILE MEDLINE
L36           0 FILE BIOSIS
L37           0 FILE BIOTECHNO
L38           0 FILE CAPLUS
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TOTAL FOR ALL FILES
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L54           0 FILE CAPLUS
L55           0 FILE EMBASE
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Searched by: Mary Hale 308-4258 CM-1 12D16

L56 0 FILE JICST-EPLUS
L57 0 FILE WPIDS

TOTAL FOR ALL FILES
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L61 3 FILE BIOTECHNO
L62 43 FILE CAPLUS
L63 6 FILE EMBASE
L64 2 FILE JICST-EPLUS
L65 0 FILE WPIDS

TOTAL FOR ALL FILES
L66 84 L25 NOT L33

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L67 50 DUP REM L66 (34 DUPLICATES REMOVED)

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L67 ANSWER 1 OF 50 CAPLUS COPYRIGHT 2001 ACS
2001:343976 Document No. 135:41360 A novel pharmacological action of ET-1 to prevent the cytotoxicity of doxorubicin in cardiomyocytes. Suzuki, Takahiko; Miyauchi, Takashi (Cardiovascular Division, Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, 305-8575, Japan). Am. J. Physiol., 280(5, Pt. 2), R1399-R1406 (English) 2001. CODEN: AJPHAP. ISSN: 0002-9513. Publisher: American Physiological Society.

AB We previously reported that cardiomyocytes produce endothelin (ET)-1 and that the tissue level of ET-1 markedly increased in failing hearts in rats with chronic heart failure. Because the level of plasma ET-1 also increased progressively in patients with breast **cancer** who received doxorubicin (Dox; Adriamycin), which possesses cardiotoxicity, we hypothesized that ET-1 plays a role in the pathophysiol. of cardiomyocytes injured by Dox. In this study, we investigated the effect of ET-1 on the cytotoxicity of Dox in primary cultured neonatal rat cardiomyocytes. The results showed that ET-1 effectively attenuated Dox-induced acute cardiomyocyte cytotoxicity (24-h incubation with Dox) evaluated by in vitro cell toxicity assay {3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay and lactate dehydrogenase release}. The cytoprotective effect of ET-1 was mediated via ETA receptors, because pretreatment with the ETA-receptor antagonist BQ 123 completely suppressed the cytoprotective effect of ET-1, whereas the ETB-receptor antagonist BQ 788 did not. The cytoprotective effect of ET-1 was abolished by pretreatment with cycloheximide or staurosporine. These results suggest that a protein mol.(s), which is synthesized de novo by the stimulation of protein kinase pathway, is involved in the cytoprotective effect of ET-1. ET-1 increased the expression of an endogenous antioxidant, manganese superoxide dismutase (Mn-SOD), in the cardiomyocytes, as demonstrated by a Western blotting anal. Pretreatment with an antisense oligodeoxyribonucleotide of Mn-SOD markedly attenuated the cytoprotective effect of ET-1 on the Dox-induced cytotoxicity. However, under conditions of prolonged incubation with Dox (48 h), ET-1 did not affect Dox-induced cardiomyocyte cytotoxicity in culture. These results suggest that ET-1 prevents the early phase of Dox-induced cytotoxicity via the upregulation of the antioxidant Mn-SOD through ETA receptors in cultured cardiomyocytes.

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L67 ANSWER 2 OF 50 CAPLUS COPYRIGHT 2001 ACS
2001:295637 Document No. 135:58920 The role of the epidermal endothelin cascade in the hyperpigmentation mechanism of lentigo senilis. Kadono, Satsuki; Manaka, Izumi; Kawashima, Makoto; Kobayashi, Takashi; Imokawa, Genji (Department of Dermatology, Tokyo Women's Medical University, Tokyo, Japan). J. Invest. Dermatol., 116(4), 571-577 (English) 2001. CODEN: JIDEAE. ISSN: 0022-202X. Publisher: Blackwell Science, Inc..

AB Little is known about the mechanism(s) underlying hyperpigmentation in lentigo senilis. We have previously reported that keratinocyte-derived endothelins are intrinsic paracrine mitogens and melanogens for human melanocytes and that they play an essential role in stimulating UV-B-induced melanogenesis. In this study, we have used immunohistochem. and reverse transcriptase polymerase chain reaction anal. to clarify the role of the endothelin cascade, including endothelin prodn., processing by endothelin-converting enzyme, and expression of the endothelin B receptor, in the hyper-pigmentary mechanism(s) involved in lentigo senilis. The no. of tyrosinase immunopos. melanocytes in lentigo senilis lesional skin was increased 2-fold over the perilesional epidermis. Immunohistochem. using antibodies to **endothelin-1** demonstrated relatively stronger staining in the lesional epidermis than in the perilesional epidermis. Reverse transcriptase polymerase chain reaction anal. concomitantly demonstrated accentuated expression of transcripts for **endothelin-1** and for the endothelin B receptor in lentigo senilis lesional skin, which was accompanied by a similar accentuated expression of tyrosinase mRNA compared with the perilesional control. The **endothelin-1**-inducible cytokine, tumor necrosis factor .alpha., was consistently upregulated in the lentigo senilis lesional epidermis as detd. at the transcriptional level and by immunostaining, whereas interleukin-1.alpha. was downregulated. In contrast, endothelin-converting enzyme 1.alpha. mRNA was not substantially increased in the lesional epidermis. These findings suggest that an accentuation of the epidermal endothelin cascade, esp. with respect to expression of endothelin and the endothelin B receptor, plays an important role in the mechanism involved in the hyperpigmentation of lentigo senilis.

L67 ANSWER 3 OF 50 CAPLUS COPYRIGHT 2001 ACS
2001:154852 Document No. 134:276108 Signaling pathways involved in the A and B receptor-mediated cortisol secretagogue effect of endothelins in the human adrenal cortex. Rebuffat, Piera; Aragona, Francesco; Tortorella, Cinzia; Malendowicz, Ludwik K.; Nussdorfer, Gastone G. (Department of Human Anatomy and Physiology, Section of Anatomy, University of Padua, Padua, I-35121, Italy). Int. J. Mol. Med., 7(3), 301-305 (English) 2001. CODEN: IJMMFG. ISSN: 1107-3756. Publisher: International Journal of Molecular Medicine.

AB Endothelins (ETs) are a family of 21-amino acid hypertensive peptides, which together with their receptors ETA and ETB are expressed in human adrenal cortex. Evidence has been provided that ETs exert a potent secretagogue effect on human adrenocortical cells, acting through both ETA and ETB receptors. Therefore, it seemed worthwhile to study the signaling cascades mediating the cortisol secretagogue effect of the two receptor subtypes. Normal adrenal glands were obtained from consenting patients undergoing unilateral nephrectomy with ipsilateral adrenalectomy for renal **cancer**. Dispersed zona fasciculata-reticularis (ZF/R) cells were obtained by collagenase digestion and mech. disaggregation. The selective activation of ETA and ETB receptors was obtained by exposing dispersed cells to ET-1 plus the ETB receptor antagonist BQ-788 and to the selective ETB receptor agonist BQ-3020, resp. ETA and ETB receptors about equally contributed to the cortisol response of dispersed ZF/R cells to ETs. The phospholipase (PL) C inhibitor U-73122 abolished ETA-mediated secretory response, but only partially prevented the ETB-mediated one. The

phosphatidylinositol 3-kinase inhibitor wortmannin and the protein kinase (PK) C inhibitor calphostin-C significantly blunted the secretory responses ensuing from the activation of both receptor subtypes, while the Ca2+-channel blocker nifedipine was ineffective. The ETB receptor-, but not the ETA receptor-mediated cortisol response was partially reversed by the cyclooxygenase (COX) inhibitor indomethacin, which when added together with U-73122 abolished it. The inhibitors of adenylate cyclase, PKA, tyrosine kinase and lipoxygenase did not affect the secretory response to the activation of either receptor subtype. ETA-receptor activation raised inositol triphosphate (IP3) prodn. from dispersed ZF/R cells, while ETB-receptor stimulation enhanced both IP3 and prostaglandin-E2 prodn. Collectively, the authors' findings indicate that ETs stimulate cortisol secretion from human ZF/R cells, acting through ETA receptors exclusively coupled with PLC/PKC-dependent pathway and ETB receptors coupled with both PLC/PKC- and COX-dependent cascades.

L67 ANSWER 4 OF 50 CAPLUS COPYRIGHT 2001 ACS
2000:869381 Document No. 134:278725 The endothelin system in human glioblastoma. Egidy, Giorgia; Eberl, Lucie Peduto; Valdenaire, Olivier; Irmler, Martin; Majdi, Rachid; Diserens, Annie-Claire; Fontana, Adriano; Janzer, Robert-Charles; Pinet, Florence; Juillerat-Jeanneret, Lucienne (INSERM U36 College de France, Paris, Fr.). Lab. Invest., 80(11), 1681-1689 (English) 2000. CODEN: LAINAW. ISSN: 0023-6837. Publisher: Lippincott Williams & Wilkins.
AB **Endothelin-1** (ET-1) is a powerful mitogenic and/or anti-apoptotic peptide produced by many **cancer** cells. To evaluate the potential role of the endothelin system in glioblastoma the authors first detd. the cellular distribution of the mRNA and proteins of the components of the endothelin system, preproendothelin-1 (PPET-1), endothelin-converting enzyme-1 (ECE-1), and ETA and ETB receptors in human glioblastoma tissue and glioblastoma cell lines. PPET-1, ECE-1, and ETA receptor were highly expressed in glioblastoma vessels and in some scattered glioblastoma areas whereas ETB receptor was mainly found in **cancer** cells. This suggests that glioblastoma vessels constitute an important source of ET-1 that acts on **cancer** cells via the ETB receptor. Four human glioblastoma cell lines expressed mRNA for all of the components of the ET-1 pathway. Bosentan, a mixed ETA and ETB receptor antagonist, induced apoptosis in these cell lines in a dose-dependent manner. Apoptosis was potentiated by Fas Ligand (APO-1L, CD95L), a pro-apoptotic peptide, only in LNZ308 cells, corresponding to the known functional Fas expression in these cell lines. LNZ308 cells also expressed the long and short forms of the cellular FLICE/caspase-8 inhibitory protein (FLIP). Bosentan and a protein kinase C inhibitor down-regulated short FLIP in these cells. ET-1 induced transient phosphorylation of extracellular signal-regulated kinase but did not induce long-term thymidine incorporation in LNZ308 glioblastoma cells. These results suggest that, in glioblastoma cells, ET-1, mainly acting via the ETB receptor, is a survival/antiapoptotic factor produced by tumor vasculature, but not a proliferation factor, involving protein kinase C and extracellular signal-regulated kinase pathways, and stabilization of the short form of FLIP.

L67 ANSWER 5 OF 50 CAPLUS COPYRIGHT 2001 ACS
2000:858205 Document No. 134:264201 Role of **endothelin-1** in neovascularization of ovarian carcinoma. Salani, Debora; Di Castro, Valeriana; Nicotra, Maria Rita; Rosano, Laura; Tecce, Raffaele; Venuti, Aldo; Natali, Pier Giorgio; Bagnato, Anna (Laboratories of Molecular Pathology and Ultrastructure, Regina Elena Cancer Institute, Rome, 00158, Italy). Am. J. Pathol., 157(5), 1537-1547 (English) 2000. CODEN: AJPAA4. ISSN: 0002-9440. Publisher: American Society for Investigative Pathology.
AB **Endothelin-1** (ET-1) is overexpressed in ovarian carcinomas and acts, via ETA receptors (ETAR), as an autocrine growth

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factor. In this study we investigate the role of ET-1 in the neovascularization of ovarian carcinoma. Archival specimens of primary (n = 40) and metastatic (n = 8) ovarian tumors were examd. by immunohistochem. for angiogenic factor and receptor expression and for microvessel d. using antibodies against CD31, ET-1, vascular endothelial growth factor (VEGF), and their receptors. ET-1 expression correlated with neovascularization and with VEGF expression. The localization of functional ETAR and ETAR mRNA expression, as detected by autoradiog. and in situ hybridization, was evident in tumors and in intratumoral vessels, whereas ETBR were expressed mainly in endothelial cells. High levels of ET-1 were detected in the majority of ascitic fluids of patients with ovarian carcinoma and significantly correlated with VEGF ascitic concn. Furthermore ET-1, through ETAR, stimulated VEGF prodn. in an ovarian carcinoma cell line, OVCA 433, by an extent comparable to hypoxia. Finally, conditioned media from OVCA 433 as well as ascitic fluids caused an increase in endothelial cell migration and the ET-1 receptor blockade significantly inhibited this angiogenic response. These findings indicate that ET-1 could modulate tumor angiogenesis, acting directly and in part through VEGF.

L67 ANSWER 6 OF 50 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
2000:237897 Document No.: PREV200000237897. **Endothelin-1** inhibits apoptosis of vascular smooth muscle cells induced by nitric oxide and serum deprivation via MAP kinase pathway. Shichiri, Masayoshi (1); Yokokura, Masaaki; Marumo, Fumiaki; Hirata, Yukio. (1) Second Department of Internal Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo, 113-8519 Japan. Arteriosclerosis Thrombosis and Vascular Biology, (April, 2000) Vol. 20, No. 4, pp. 989-997. ISSN: 1079-5642. Language: English. Summary Language: English.

AB Endothelin (ET)-1, an endothelium-derived vasoconstrictor and mitogen, acts as an antiapoptotic factor against serum deprivation-induced apoptosis of endothelial cells and fibroblasts but enhances apoptosis of some **cancer** cells. In the present study, we examined whether nitric oxide (NO) and ET-1 modulate apoptosis of rat vascular smooth muscle cells (VSMCs) via the mitogen-activated protein (MAP) kinase pathway. Both serum deprivation and NO donors (FK409 and SNAP) caused apoptosis of VSMCs, as demonstrated by TdT-mediated dUTP-biotin nick end-labeling, appearance of fragmented DNA, and induction of caspase-3 activity. ET-1 dose-dependently antagonized apoptosis induced by serum deprivation and NO donors. A selective ETA receptor antagonist (BQ123) and a nonselective ETA/B receptor antagonist (TAK044), but not a selective ETB receptor antagonist (BQ788), inhibited the antiapoptotic effect of ET-1, indicating that the antiapoptotic effect of ET-1 is mediated via the ETA receptor. ET-1 activated MAP kinase, whose effect was inhibited by FK409. Transfection with an unphosphorylated wild-type MAP kinase kinase-1 (MAPKK-1) or its constitutively activated mutant protected VSMCs against apoptosis induced by serum deprivation and NO donors. Inhibition of MAP kinase activity with PD98059, a specific inhibitor of MAPKK-1, or by transfection of a dominant-negative MAPKK-1 mutant antagonized the antiapoptotic effect of ET-1, suggesting the involvement of MAP kinase in the antiapoptotic effect. The potent inhibitory effect of ET-1 on apoptosis of VSMCs induced by serum deprivation and NO suggests that the counterbalance between the 2 endothelium-derived factors contributes to the process of vascular remodeling by determining VSMC survival and death, respectively, via a common MAP kinase pathway.

L67 ANSWER 7 OF 50 MEDLINE DUPLICATE 2
2001038045 Document Number: 20490522. PubMed ID: 11034585. Stimulation of colorectal **cancer** cell line growth by ET-1 and its inhibition by ET(A) antagonists. Ali H; Loizidou M; Dashwood M; Savage F; Sheard C; Taylor I. (Department of Surgery, Royal Free and University College Medical School, London, UK.) GUT, (2000 Nov) 47 (5) 685-8. Journal code:

Searched by: Mary Hale 308-4258 CM-1 12D16

FVT. ISSN: 0017-5749. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: The vasoactive peptide **endothelin 1** (ET-1) acts via two receptors, **endothelin receptors** A (ET(A)) and B (ET(B)). ET-1 is overexpressed by human **cancers** in vivo and in vitro and may be mitogenic for **cancer** cells. METHOD: To elucidate if ET-1 is a growth regulator the following were investigated in human colorectal **cancer** cell lines (LIM1215 and HT29): ET-1 production by ELISA; ET receptor expression using radioligand autoradiographic techniques; and responsiveness to ET-1, and to ET(A) and ET(B) antagonism by growth measurements. RESULTS: ET-1 was produced by LIM1215 and HT29 cells (21.3 and 41.7 fmol/ml/10(6) cells (24 hours); 22.6 and 71.7 fmol/ml/10(6) cells (48 hours), respectively). ET(A) and ET(B) receptors were expressed by both cell lines. Addition of ET-1 resulted in a dose dependent increase in cell numbers which was significant at 10(-8)-10(-9) M for LIM1215, with the greatest increase at 10(-8) M (32.7% and 28.4% increase above controls at 48 hours and 72 hours; $p<0.05$) and at 10(-8)-10(-9) M for HT29, with the greatest increase at 10(-9) M (13.4% and 15.7% increase above controls at 48 hours and 72 hours; $p<0.05$). ET(A) antagonists BQ123 and BQ610, but not the ET(B) antagonist BQ788, inhibited ET-1 induced proliferation of both LIM1215 and HT29 ($p<0.05$). CONCLUSION: ET-1 can stimulate the proliferation of colorectal **cancer** cell lines via the ET(A), but not the ET(B), receptor.

L67 ANSWER 8 OF 50 CAPLUS COPYRIGHT 2001 ACS

2000:290083 Document No. 133:56838 Studies on the expression of endothelin, its receptor subtypes, and converting enzymes in lung **cancer** and in human bronchial epithelium. Ahmed, Samreen I.; Thompson, James; Coulson, Judy M.; Woll, Penella J. (Cancer Research Campaign, Academic Department of Clinical Oncology, Nottingham City Hospital, University of Nottingham, Nottingham, UK). Am. J. Respir. Cell Mol. Biol., 22(4), 422-431 (English) 2000. CODEN: AJRBEL. ISSN: 1044-1549. Publisher: American Thoracic Society.

AB Lung **cancer**, particularly small cell lung **cancer** (SCLC), is characterized by prodn. of numerous peptides and their resulting clin. syndromes. Such peptides can act as autocrine growth factors for these tumors. In this study, we investigated the role of endothelin (ET)-1 in lung **cancer**. Using reverse transcription/polymerase chain reaction (RT-PCR), ELISA, and immunocytochem., we screened a panel of lung **cancer** cell lines for ET-1, its receptors, and endothelin converting enzyme-1 (ECE-1), which generates the active form of ET-1. ET-1 mRNA was expressed in five of seven SCLC, four of four non-small cell lung **cancer** (NSCLC), and human bronchial epithelial (HBE) cells. The intracellular isoform of ECE-1, important in processing ET-1 if an autocrine growth loop is to function, was down-regulated in the lung **cancer** cell lines as compared with expression of the extracellular isoform. Endothelin A receptor (ETAR), which mediates the mitogenic effects of ET-1 in prostate and **ovarian cancer**, was upregulated in HBE cells compared with expression in three of seven SCLC and two of four NSCLC cell lines. Endothelin B receptor (ETBR) was more widespread, being expressed in seven of seven SCLC, four of four NSCLC, and the HBE cells. We used flow cytometry to measure mobilization of intracellular calcium as a functional assay for the ETAR. These data concurred with the RT-PCR results, indicating that the ETAR was downregulated or was involved in an alternative signal transduction pathway in lung **cancer**, and no evidence of functional receptor mediating an autocrine growth loop was found. From our study, the data do not support the putative functional autocrine growth role of ET-1 in lung **cancer**. We propose instead that ET-1 may act as a paracrine growth factor for surrounding epithelial and endothelial cells via alternative pathways, promoting angiogenesis and stromal growth.

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L67 ANSWER 9 OF 50 MEDLINE DUPLICATE 3
2001127507 Document Number: 20527865. PubMed ID: 11078428. Expression of **endothelin receptors** in human myometrium during pregnancy and in uterine leiomyomas. Honore J C; Robert B; Vacher-Lavenu M C; Chapron C; Breuiller-Fouche M; Ferre F. (National Institute of Health and Medical Research INSERM U.361, Paris, France.) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (2000 Nov) 36 (5 Suppl 1) S386-9. Journal code: K78. ISSN: 0160-2446. Pub. country: United States. Language: English.

AB The distribution of mRNAs for endothelinA and B (ET(A) and ET(B)) receptors and their binding properties was studied in human nonpregnant and pregnant term myometrium and in uterine leiomyomas. ET(A)- and ET(B)-receptors functionally coupled to phospholipase C (PLC) coexisted in myometrial tissues, but only the functional ET(A)-receptor subtype was detected in leiomyomas. ET(A)-receptor mRNA and three other spliced variants were distributed in all tissue studied. We reported an increase in the proportion of ET(A)-receptors coupled to PLC in term pregnant myometrium when compared to nonpregnant tissue. These results suggest that upregulation of the myometrial ET(A)-receptors may account for or contribute to the control of normal development and growth of human myometrium during pregnancy. They also support a pathological role for the **endothelin-1** (ET-1)/ET(A)-receptor system in leiomyoma development.

L67 ANSWER 10 OF 50 CAPLUS COPYRIGHT 2001 ACS
2000:301700 Document No. 133:236054 Proliferative role of **endothelin -1** in human uterine leiomyoma cells. Li, Guiyun; Xin, Xiaoyan; Qian, Jixian; Zhu, Yaping (Department of Obstetrics and Gynecology, Xijing Hospital, Fourth Military Medical University, Xi'an, 710033, Peop. Rep. China). Disi Junyi Daxue Xuebao, 21(3), 363-365 (Chinese) 2000. CODEN: DJDXEG. ISSN: 1000-2790. Publisher: Disi Junyi Daxue Xuebao Bianjibu.

AB The effects of **endothelin-1** (ET-1) on human uterine leiomyoma cell growth and proliferation were studied. The human uterine leiomyoma cells were harvested, digested and cultured. The cells of passage 4-6 were routinely used for study after the identification with .alpha.-actin antibody. ET-1 at the concn. of 1.0 .mu.mol L-1 was added into the culture, whereby the cell no. and 3H-TdR incorporation were recorded 1-4 days after the stimulation. 125I-ET-1 radio binding and immunohistol. were used to det. the expression of ETA and ETB proteins. The cultured cells stimulated by ET-1 significantly increased, which was consistent with the trends of 3H-TdR incorporation. The expression of ETA protein was detected in all the cultured cells, its gradual increase after ET-1 stimulation was obsd. Nevertheless, the protein expression of ETB was not probed even though ET-1 was applied. These results indicated that ET-1 promoted human uterine leiomyoma cell growth and proliferation in culture. Only ETA receptors were present in the cells. ET-1 induced and potentiated ETA increase.

L67 ANSWER 11 OF 50 CAPLUS COPYRIGHT 2001 ACS
2000:776128 Document No. 134:65912 Endothelin receptor blockade potentiates FasL-induced apoptosis in colon carcinoma cells via the protein kinase C pathway. Eberl, Lucie Peduto; Egidy, Giorgia; Pinet, Florence; Juillerat-Jeanneret, Lucienne (Institute of Pathology, University of Lausanne, Lausanne, Switz.). J. Cardiovasc. Pharmacol., 36(5, Suppl. 1), S354-S356 (English) 2000. CODEN: JCPCDT. ISSN: 0160-2446. Publisher: Lippincott Williams & Wilkins.

AB An imbalance between proliferation and apoptosis is important in tumor progression. **Endothelin-1** (ET-1) has vasoconstricting and mitogenic activities and may be involved in apoptosis regulation. We found that ET-1 and FasL systems were co-localized in human colon tumors and that ET-1 was secreted by human (HT-29, SW480) and rat (PROb, REGb)

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colon carcinoma cell lines. Bosentan, a mixed endothelin-A- and -B- (ETA/ETB) receptor antagonist, potentiated FasL- (APO-1, CD95)-induced apoptosis in these cells. The specific inhibition of enzymes involved in ceramide prodn. did not restore survival of cells exposed to FasL and bosentan. Inhibition of PKC with bisindolylmaleimide IX enhanced FasL-induced apoptosis in HT-29, PROb and REGb cells in the absence of bosentan. These results suggest that ET-1 is an autocrine survival factor able to protect colon carcinoma cells against FasL-induced apoptosis, involving the protein kinase C (PKC) but not the sphingomyelin-ceramide signaling transduction pathways.

L67 ANSWER 12 OF 50 CAPLUS COPYRIGHT 2001 ACS

2000:264725 Document No. 133:162439 Endothelin receptor blockade potentiates FasL-induced apoptosis in rat colon carcinoma cells. Eberl, Lucie Peduto; Valdenaire, Olivier; Saintgiorgio, Valerie; Jeannin, Jean-Francois; Juillerat-Jeanneret, Lucienne (Institute of Pathology, University of Lausanne, Lausanne, CH1011, Switz.). Int. J. Cancer, 86(2), 182-187 (English) 2000. CODEN: IJCNAW. ISSN: 0020-7136. Publisher: Wiley-Liss, Inc..

AB Imbalanced proliferation and apoptosis is important in tumor progression. Endothelin (ET)-1, a 21-amino-acid peptide with vasoconstricting and mitogenic activities, has been shown to be involved in the regulation of apoptosis. Progressive and regressive rat colon (PROb and REGb cells) carcinoma cell lines express the components of the ET-1 system (preproET-1, ET-converting enzyme and ET-receptors) and secrete ET-1. These cells also express the Fas(APO-1, CD95)/FasL system, but are resistant to FasL-induced apoptosis. We thus addressed the role of ET-1 in FasL-dependent cell death. Bosentan, a mixed ETA/ETB receptor antagonist, potentiated FasL-induced apoptosis in these cells. At low concns. (10-13 to 10-10 M), ET-1 dose-dependently reversed bosentan-induced apoptosis. Bosentan sensitization to FasL-induced apoptosis was not mediated by increased expression of Fas receptor and was blocked by the caspase inhibitor zVAD-fmk. The specific inhibition of enzymes involved in ceramide prodn. did not restore survival of cells exposed to FasL and bosentan. Our results suggest that ET-1 is a survival factor able to protect in vitro colon carcinoma cells against FasL-induced apoptosis.

L67 ANSWER 13 OF 50 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 4

2001:18277 Document No.: PREV200100018277. 'Irreversible' **endothelin -1** binding does not prohibit ABT-627 from reversing **endothelin-1**-induced effects. Chiou, William J.; Wessale, Jerry L.; von Geldern, Thomas; Opgenorth, Terry J.; Wu-Wong, Jinshyun R. (1). (1) Abbott Laboratories, 5440 Patrick Henry Drive, Santa Clara, CA, 95054 USA. Journal of Cardiovascular Pharmacology, (2000) Vol. 36, No. 5 Supplement 1, pp. S48-S52. print. ISSN: 0160-2446. Language: English. Summary Language: English.

AB **Endothelin-1** (ET-1) is thought to play a role in a wide range of pathological conditions. One of the distinct characteristics of ET-1 is its long-lasting vasoconstrictor action, which is presumably caused by the irreversible binding of ET-1 to ET receptors and by the functional effects of internalized ET receptors. ABT-627 is a potent endothelin-A (ETA)-selective antagonist with a Ki, value at 0.034 nM for the human ETA receptor, and is currently being used in clinical studies for **prostate cancer**. Unlike ET-1, the binding of 125I-labeled ABT-627 to human ETA receptors expressed in Chinese hamster ovary (CHO) cells is reversible, and the dissociation half-life for the ligand/receptor complex is 2 h. Interestingly, the binding of both ET-1 and ABT-627 to the ETA-receptor results in partial receptor internalization but only ET-1 is capable of triggering intracellular functional responses. Although ABT-627 binding to membranes is more reversible than ET-1 binding, ABT-627 is able to reverse an ET-1-induced

contraction in rat aortic rings in a dose-dependent manner, and at 1 muM produces nearly complete reversal of the constrictor effects of 10 nM ET-1 within 60 min. Similarly, in vivo studies show that ABT-627 (0.01 and 0.1 mg/kg/min i.v.) reverses the ET-1-induced increase in arterial pressure in anesthetized, ganglionic-blocked rats, and after 60 min, ABT-627 essentially normalizes pressure. Our data show that ABT-627 is capable of reversing an established response induced by ET-1 and is useful in reversing pathological conditions involving ET-1.

L67 ANSWER 14 OF 50 MEDLINE DUPLICATE 5

2000283541 Document Number: 20283541. PubMed ID: 10822048. Enhanced endothelin ET(B) receptor down-regulation in human tumor cells. Drimal J; Drimal J Jr; Drimal D. (Institute of Experimental Pharmacology, Cardiovascular Research Laboratory, Slovak Academy of Sciences, Dubravska cesta 9, 842 16, Bratislava, Slovak Republic.. exfadrim@savba.sk) . EUROPEAN JOURNAL OF PHARMACOLOGY, (2000 May 12) 396 (1) 19-22. Journal code: EN6; 1254354. ISSN: 0014-2999. Pub. country: Netherlands. Language: English.

AB The characteristics of specific binding of human [125I]Tyr(13)-**endothelin**-(1-21), [125I]-Tyr(13)-Suc-[Glu(9),Ala(11, 15)]-endothelin-(8-21), ([125I]IRL-1620) and endothelin ET(A) receptor antagonist [125I]Tyr(3)-(N-[(hexahydro-1H-azepin-1-yl)carbonyl]-L-Leu]-1Me)-D-Trp ([125I]PD151242) (number of sites and their affinity) and proliferation responses to exogenous endothelin receptor agonists (**endothelin-1** and the endothelin ET(B) receptor-selective, truncated N-acetyl-[Ala(11,15)]-endothelin-(6-21) analogue BQ3020) were determined in cultured human fibroblasts and in tumorigenic HeLa cells. The cells were pre-incubated with equimolar concentrations of human **endothelin-1** or its truncated analogue BQ3020. After pre-incubation (2 h), both peptides induced down-regulation of surface-membrane **endothelin-1** receptors. This process was specific for endothelin ET(B) receptors and was much more intensive in tumorigenic cells. BQ3020, acting mostly through its C-terminus, induced nearly maximal endothelin ET(B) receptor down-regulation in HeLa cells. Staurosporine, a wide spectrum protein kinase inhibitor, significantly reduced, and N-[N-[N-[2, 6-dimethyl-1piperidinyl)carbonyl]-4-Me-L-Leu]-1-(methoxycarbonyl)- D-t ryptophanyl]-D-norleucine (BQ788), an endothelin ET(B) receptor antagonist, attenuated the down-regulation of **endothelin receptors** induced by endothelin receptor agonists. The down-regulation of endothelin ET(B) receptors was prevented by pre-incubation of the cells with the lysosomal enzyme blocker chloroquine. The **endothelin-1**-induced cell proliferation was attenuated by pre-incubation of the cells with the non-selective endothelin receptor antagonist Ac-D-10,11-dihydro-5H-dibenzo[a,d] cycloheptene-glycine-3,3-D-diphenyl-Ala-Leu-Asp-Ile-Ile-Trp (PD142893) and it was only partially reduced by the endothelin ET(A) receptor-selective endothelin antagonist PD151242.

L67 ANSWER 15 OF 50 CAPLUS COPYRIGHT 2001 ACS

1999:654633 Document No. 132:91570 Endothelins and their receptors in cirrhotic and neoplastic livers of Canadian and Chinese populations. Cai, L.; Wang, G. J.; Mukherjee, K.; Xu, Z. L.; Khalil, M.; Cherian, M. G.; Chakrabarti, S. (Department of Pathology, The University of Western Ontario, London, ON, N6A 5C1, Can.). Anticancer Res., 19(3B), 2243-2247 (English) 1999. CODEN: ANTRD4. ISSN: 0250-7005. Publisher: International Institute of Anticancer Research.

AB Background: Endothelins (ETs) are 21 amino acid peptides with widespread tissue distribution and functions. In this study, we retrospectively investigated immunoreactive ET-1, ET-3 as well as ET receptors by ligand binding and autoradiog. in hepatic cirrhosis and **neoplasms**. Formalin fixed paraffin embedded tissues from 30 hepatocellular carcinomas

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(HCC), 4 fibrolamellar carcinomas (FLC), and 7 liver metastatic adenocarcinomas (Ad) from colon were collected from the Pathol. Department of London Health Science Center. Adjacent cirrhotic livers were obtained from 17 cases and adjacent normal liver was present in 12 cases. In addn., 15 HCCs, 6 cirrhotic and 8 normal livers were obtained from Normal Bethune University for Medical Sciences in China. The slides were stained for ET-1 and ET-3 with a polyclonal antibody and scored. Autoradiog. localization of ET-receptors with 125I-ET-1 was carried out in some of the cases. In the normal liver, hepatocytes, biliary epithelium, vascular endothelium and smooth muscle cells were pos. for both ET-1 and ET-3. Higher immunoreactivity for ET-1 and ET-3 was seen in cirrhosis. HCCs showed variation in immunoreactivity, with overall scoring not different from normal livers. FLCs showed consistent higher immunoreactivity for both ET-1 and ET-3, while in Ads the immunoreactivity was decreased. Increased ET-receptors, representing both ETA and ETB subtypes were seen in both cirrhosis and in HCC. Alterations in both ETs and their receptors were found in cirrhosis and neoplastic liver diseases.

L67 ANSWER 16 OF 50 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 6

1999:489008 Document No.: PREV199900489008. Paracrine regulation of **ovarian cancer** by endothelin. Moraitis, S.; Miller, W. R.; Smyth, J. F.; Langdon, S. P. (1). (1) Imperial Cancer Research Fund Medical Oncology Unit, Western General Hospital, Edinburgh, EH4 2XU UK. European Journal of Cancer, (Sept., 1999) Vol. 35, No. 9, pp. 1381-1387. ISSN: 0959-8049. Language: English. Summary Language: English.

AB Previous studies have demonstrated that endothelin (ET) isoforms (ET-1, ET-2 and ET-3) can act in an autocrine manner in **ovarian cancer** while in breast **cancer** their role has been proposed to be that of a paracrine mitogen. To explore the possibility that endothelin isoforms might function not only as autocrine regulators but also as paracrine mitogens in **ovarian cancers**, we investigated their effects on the growth of ovarian fibroblasts derived from ovarian carcinomas, the interaction between ovarian carcinoma and fibroblast cells and the location of the isoform expression in primary ovarian tumours. ET-1, ET-2 and ET-3 stimulated the growth of three ovarian fibroblast cell lines at concentrations ranging from 10-12 M to 10-7 M. Inhibition of 125I-ET binding by the ETA receptor antagonist BQ123 and the ETB receptor antagonist BQ788 suggested the presence of both types of ET receptors in fibroblast cells. In the absence of ET-1, neither BQ 123 nor BQ 788 inhibited growth. However, both antagonists inhibited ET-1 stimulated growth suggesting the involvement of both receptor types in ET-1 growth regulation. In contrast to carcinoma cells which secrete measurable levels of ET-1, fibroblast cell lines did not secrete detectable protein. Co-culture experiments (using porous membrane insert wells) of fibroblasts with carcinoma cells demonstrated that growth of both populations of cells was increased compared with either grown in isolation. In this system, growth of the fibroblast cell line was partially inhibited by both BQ123 and BQ788, whilst growth of the PE014 carcinoma cell line was inhibited by only BQ123. RT-PCR measurements detected the presence of the ETA receptor subtype in 10/10 primary **ovarian cancers** but the presence of ETB receptor in only 6/10 **cancers**. Using specific antibodies, ET-1 was found in 11/15, ET-2 in 5 of 7 and ET-3 in 5/7 primary **ovarian cancers** predominantly in the epithelial cells but with some stromal expression. These data indicate that the ET isoforms may stimulate growth of the fibroblast population within an **ovarian cancer** in addition to stimulating the epithelial cells and since the ETs are expressed in the majority of **ovarian cancers**, this paracrine effect may contribute to the overall growth of the tumour.

L67 ANSWER 17 OF 50 MEDLINE DUPLICATE 7

Searched by: Mary Hale 308-4258 CM-1 12D16

1999316361 Document Number: 99316361. PubMed ID: 10383740. Downregulation of endothelin B receptor in human **melanoma** cell lines parallel to differentiation genes. Eberle J; Weitmann S; Thieck O; Pech H; Paul M; Orfanos C E. (Department of Dermatology, University Medical Center Benjamin Franklin, The Free University of Berlin, Germany.) JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1999 Jun) 112 (6) 925-32. Journal code: IHZ; 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.

AB Normal human melanocytes have been shown to respond to the signal peptide endothelin by increased proliferation and melanin formation. Contradictory findings, however, have been reported about which of the two **endothelin receptors** (EDNRA or EDNRB) is expressed in normal melanocytes and **melanoma** cells. Moreover it was not clear whether malignant cells differ from their normal precursors in this respect. Screening a melanocyte cDNA library for genes downregulated in **melanomas** identified clones specific for EDNRB. Northern blots proved that the corresponding mRNA is generally expressed in cultures of human cutaneous melanocytes and congenital melanocytic nevus cells. In 16 of 17 **melanoma** cell lines, however, the expression of EDNRB mRNA was strongly downregulated. EDNRA was only weakly expressed and detectable by northern blotting in 12 of 17 cultures of benign melanocytic cells and four of 17 **melanoma** cell lines. Nested reverse transcriptase-polymerase chain reaction proved several **melanoma** cell lines to be completely negative for EDNRA expression. Gene deletion as the cause of missing endothelin receptor expression was ruled out by genomic Southern blots. Receptor binding assays confirmed RNA data revealing 1.6 x 105 **endothelin-1** binding sites per cell for a melanocyte culture and between 8.7 x 104 and 400 sites per cell for **melanoma** cell lines. Expression of pigmentation genes coding for tyrosinase, TRP-1 and TRP-2 correlated positively with that of EDNRB but negatively with EDNRA expression. EDNRB but not EDNRA expression is therefore typical for melanocytic cells, and downregulation of EDNRB seems to be an important characteristic of **melanoma** cells possibly related to malignancy or apoptosis.

L67 ANSWER 18 OF 50 MEDLINE

1999372849 Document Number: 99372849. PubMed ID: 10445677. Increased endothelin-receptor density in myxomatous canine mitral valve leaflets. Mow T; Pedersen H D. (Department of Clinical Studies, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark.) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1999 Aug) 34 (2) 254-60. Journal code: K78; 7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.

AB In dogs and humans, myxomatous mitral valve disease results in mitral valve prolapse and mitral regurgitation. Diseased leaflets display endothelial damage, which in turn might lead to subendothelial growth through release of paracrine mediators such as **endothelin-1**. The aim of the study was to investigate the presence and distribution of **endothelin receptors** and relate these to the presence and severity of myxomatous valve disease in the dog. Valves with clear macroscopic signs of disease were taken at postmortem from five old dogs. Control valves without macroscopic signs of disease were taken from five young dogs. **Endothelin receptors** in the leaflets were examined by using radiolabeled **endothelin-1** detected by autoradiography. The endothelin-receptor density was graded semiquantitatively. To determine disease severity, adjacent sections stained with periodic acid-Schiff (PAS)/Alcian blue were examined histologically. The leaflet thickness was measured, and the mucopolysaccharide deposition, collagen degeneration, and fibrosis were graded semiquantitatively. Diseased areas displayed high endothelin-receptor densities; normal-looking areas showed low densities. The endothelin-receptor density within as well as on the leaflets correlated positively with all four measures of disease severity in the distal most affected third of the cusps, suggesting that endothelin plays

a pathogenetic role in canine myxomatous mitral valve disease.

L67 ANSWER 19 OF 50 CAPLUS COPYRIGHT 2001 ACS
1999:194657 Document No. 131:4144 Upregulation of **endothelin 1** and its precursor by IL-1.beta., TNF-.alpha., and TGF-.beta. in the PC3 human **prostate cancer** cell line. Le Brun, Gaelle; Aubin, Philippe; Soliman, Hany; Ropiquet, Frederic; Villette, Jean-Marie; Berthon, Philippe; Creminon, Christophe; Cussenot, Olivier; Fiet, Jean (Laboratoire de Biologie Hormonale, Hopital Saint-Louis, Paris, 75475, Fr.). Cytokine, 11(2), 157-162 (English) 1999. CODEN: CYTIE9. ISSN: 1043-4666. Publisher: Academic Press.

AB Increasing evidence indicates that **endothelin 1** (ET-1) is implicated in prostate tumor progression. However, data on ET-1 regulation in human prostate and **prostate cancer** cell lines are lacking. In this study, regulation of ET-1 and its precursor big ET-1, using PC3 cells, a human bone metastatic prostatic carcinoma cell line, was addressed. ET-1 and big ET-1 assays demonstrated greater secretion of both peptides in the presence of 10% fetal calf serum (FCS) as compared with 0.5% FCS. Incubation of PC3 cells in the absence and presence of various cytokines and growth factors known to be implicated in prostate stroma-epithelium interactions, revealed that IL-6, FGF7/KGF and FGF2/bFGF had no effect on ET-1 and big ET-1 secretion, whereas interleukin 1.beta. (IL-1.beta.), tumor necrosis factor .alpha. (TNF-.alpha.) and transforming growth factor .beta. (TGF-.beta.) stimulated their secretion in a concn.-dependent manner. Binding expts. indicated the presence of specific ET-1 receptors in PC3 cells: Kdapp=1.1.times.0.2.times.10-10M, Bmax=2660.+-.390 sites/cell. Data anal. demonstrated the presence of only the ETA receptor subtype in PC3 cells. In conclusion, our results indicate that the implication of ET-1 in **prostate cancer** is likely to be mediated via paracrine/autocrine control of cell factors. (c) 1999 Academic Press.

L67 ANSWER 20 OF 50 CAPLUS COPYRIGHT 2001 ACS
2000:15082 Document No. 132:306441 Stimulation of pancreatic **cancer** growth by hypoxia is mediated via endothelin-A receptors. Hotz, Hubert G.; Reber, Howard A.; Sanghavi, Premal C.; Yu, Tina; Hotz, Birgit; Buechler, Peter; Hines, O. Joe (Division of General Surgery, School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA). Surg. Forum, 50, 88-90 (English) 1999. CODEN: SUFOAX. ISSN: 0071-8041. Publisher: American College of Surgeons.

AB The aim of this study was to evaluate whether pancreatic **cancer** cell lines express ET-1 and the **endothelin receptors** A and B (ETAR and ETBR). Furthermore, the effect of selective endothelin receptor blockade on growth of pancreatic **cancer** cells was detd. in vitro under normoxic and hypoxic conditions. This study demonstrated that pancreatic **cancer** cell lines express ET-1 mRNA, and all but one show expression of the ETAR that is relatively specific for ET-1. Selective blockade of the ETAR significantly reduced in vitro proliferation of pancreatic **cancer** cells in a dose-dependent manner. This redn. of proliferation was more prominent under hypoxic conditions, suggesting that hypoxia-induced growth of pancreatic **cancer** cells is, at least in part, mediated by ET-1 via ETA receptors.

L67 ANSWER 21 OF 50 CAPLUS COPYRIGHT 2001 ACS
1998:209156 Document No. 128:306432 Cloning and characterization of a novel endothelin receptor subtype in the avian class. Lecoin, Laure; Sakurai, Takeshi; Ngo, Minh-Triet; Abe, Yoichiro; Yanagisawa, Masashi; Le Douarin, Nicole M. (Institut d'Embryologie Cellulaire Moleculaire Centre National Recherche Scientifique, College de France, Nogent sur Marne, Fr.). Proc. Natl. Acad. Sci. U. S. A., 95(6), 3024-3029 (English) 1998. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

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AB We report the cloning by reverse transcriptase-PCR of an avian cDNA encoding a subtype of endothelin receptor (EDNR), which we have called EDNRB2, because its deduced amino acid sequence is more closely related to that of EDNRB than to either the mammalian EDNRA or to the Xenopus EDNRC. Its expression pattern differs from that of the classical avian EDNRB because it is strongly expressed in melanoblasts and melanocytes. EDNRB2 transcripts are also abundant in the liver and kidney. Our pharmacol. studies showed that EDNRB2 binds with similar affinity to EDN 1, EDN 2, and EDN 3, further confirming that this receptor belongs to the B type, although it displays a low affinity for sarafotoxin-c, a known EDNRB-selective agonist.

L67 ANSWER 22 OF 50 MEDLINE DUPLICATE 8

1999036055 Document Number: 99036055. PubMed ID: 9820169. Truncated human endothelin receptor A produced by alternative splicing and its expression in **melanoma**. Zhang Y F; Jeffery S; Burchill S A; Berry P A; Kaski J C; Carter N D. (Department of Cardiological Sciences, St George's Hospital Medical School, London, UK.) BRITISH JOURNAL OF CANCER, (1998 Nov) 78 (9) 1141-6. Journal code: AV4; 0370635. ISSN: 0007-0920. Pub. country: SCOTLAND: United Kingdom. Language: English.

AB In this study, reverse transcriptase polymerase chain reaction was used to amplify human **endothelin receptor** A (ETA) and **ETB** receptor mRNA. A truncated ETA receptor transcript with exons 3 and 4 skipped was found. The skipping of these two exons results in 109 amino acids being deleted from the receptor. The truncated receptor was expressed in all tissues and cells examined, but the level of expression varied. In **melanoma** cell lines and **melanoma** tissues, the truncated receptor gene was the major species, whereas the wild-type ETA was predominant in other tissues. A 1.9-kb ETA transcript was identified in **melanoma** cell lines by Northern blot, which was much smaller than the transcript in heart and in other tissues reported previously (4.3 kb). The cDNA coding regions of the truncated and wild-type ETA receptors were stably transfected into Chinese hamster ovary (CHO) cells. The truncated ETA receptor-transfected CHO cells did not show binding affinity to **endothelin 1** (ET-1) or endothelin 3 (ET-3). The function and biological significance of this truncated ETA receptor is not clear, but it may have regulatory roles for cell responses to ETs.

L67 ANSWER 23 OF 50 CAPLUS COPYRIGHT 2001 ACS

1999:399830 Document No. 131:154002 Endothelin signalling in the development of neural crest-derived melanocytes. Opdecamp, Karin; Kos, Lidia; Arnheiter, Heinz; Pavan, William J. (Laboratory of Developmental Neurogenetics, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, 20892, USA). Biochem. Cell Biol., 76(6), 1093-1099 (English) 1998. CODEN: BCBIEQ. ISSN: 0829-8211. Publisher: National Research Council of Canada.

AB In both mice and humans, mutations in the genes encoding the endothelin B receptor and its ligand endothelin 3 lead to deficiencies in neural crest-derived melanocytes and enteric neurons. The discrete steps at which endothelins exert their functions in melanocyte development were examd. in mouse neural crest cell cultures. Such cultures, kept in the presence of fetal calf serum, gave rise to cells expressing the early melanoblast marker Dct even in the absence of the phorbol ester tetradecanoyl phorbol acetate (TPA) or endothelins. However, these early Dct+ cells did not proliferate and pigmented cells never formed unless TPA or endothelins were added. In fact, endothelin 2 was as potent as TPA in promoting the generation of both Dct+ melanoblasts and pigmented cells, and **endothelin 1** or endothelin 3 stimulated the generation of melanoblasts and of pigmented cells to an even greater extent. The inhibition of this stimulation by the selective endothelin B receptor antagonist BQ-788 (N-cis-2,6-dimethylpiperidinocarbonyl-L-.alpha.-

methylleucyl-D-1-methoxycarbonyltryptophanyl-D-norleucine) suggested that the three endothelins all signal through the endothelin B receptor. This receptor was indeed expressed in Dct+ melanoblasts, in addn. to cells lacking Dct expression. The results demonstrate that endothelins are potent stimulators of melanoblast proliferation and differentiation.

L67 ANSWER 24 OF 50 MEDLINE DUPLICATE 9
1998257890 Document Number: 98257890. PubMed ID: 9595534.
Endothelin receptors and angiotensin II receptors in tumor tissue. Kohzuki M; Tanda S; Hori K; Yoshida K; Kamimoto M; Wu X M; Sato T. (Section of Internal Medicine and Disability Prevention, Tohoku University Graduate School of Medicine, Sendai, Japan.) JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, (1998) 31 Suppl 1 S531-3. Journal code: K78; 7902492. ISSN: 0160-2446. Pub. country: United States. Language: English.
AB In **cancer** chemotherapy, selective enhancement of drug delivery to tumor tissue is essentially important for increase of chemotherapeutic effects. An attenuated vasoconstrictive response to angiotensin II (Ang II) in tumors and a marked increase in tumor blood flow were observed compared with normal tissues during systemic hypertension induced by Ang II infusion. The phenomenon was absent when hypertension was provoked by **endothelin-1** (ET-1). We assessed this response to characterize ET receptor and Ang II receptor density and affinity in normal and tumor tissues. The tumor cell line LY80 was transplanted to the skin in nude rats. Four weeks later the rats were sacrificed. [125I] ET-1 and [125I Sar1, Ile8]-Ang II were used to map the receptors for ET and Ang II in rat tissues using computerized in vitro autoradiography. A moderately high density of ET receptors, (ETB > ETA) was found in tumors. The Ang II receptors were markedly reduced in tumor tissues without changes in the affinity. These results suggest that the decrease in Ang II receptors but not ET receptors in tumors may explain the hemodynamic effect of Ang II-induced hypertension and ET-induced hypertension on tumor blood flow.

L67 ANSWER 25 OF 50 MEDLINE
1998012118 Document Number: 98012118. PubMed ID: 9351753. EndothelinA receptors in human uterine leiomyomas. Breuiller-Fouche M; Vacher-Lavenu M C; Fournier T; Morice P; Dubuisson J B; Ferre F. (Institut National de la Sante et de la Recherche Medicale INSERM U.361, The Service de Gynecologie Obstetrique II a orientation gynecologique, Pavillon Baudelocque, Paris, France.. u361@cochin.inserm.fr) . OBSTETRICS AND GYNECOLOGY, (1997 Nov) 90 (5) 727-30. Journal code: OC2; 0401101. ISSN: 0029-7844. Pub. country: United States. Language: English.
AB OBJECTIVE: To determine if there are **endothelin receptors** on human uterine leiomyomas. METHODS: Samples of leiomyomas from eight patients were analyzed for [iodine (I)-125] **endothelin-1** binding. Several subtype-selective ligands were used to determine the endothelin receptor population. RESULTS: Binding of [125I]**endothelin-1** to uterine leiomyoma membranes was specific and saturable, with a mean +/- dissociation constant 85.5 +/- 8.4 pM. Competition binding studies showed that the order of potency was **endothelin-1** > endothelin-3, which was consistent with the presence of the endothelinA receptor subtype. Binding of [125I]**endothelin-1** was displaced by an endothelinA-selective antagonist, but not by sarafotoxin 6c, an endothelinB-selective agonist. An endothelins-selective ligand was not specifically bound to leiomyoma. CONCLUSION: These results indicate that only endothelinA receptors are present in human uterine leiomyomas. We speculate that **endothelin-1** may act through these endothelinA receptors to influence the development or regulation of hypertrophy and proliferation of the human myometrium during pregnancy and in uterine disorders like leiomyomas.

Searched by: Mary Hale 308-4258 CM-1 12D16

L67 ANSWER 26 OF 50 CAPLUS COPYRIGHT 2001 ACS
1997:371225 Document No. 127:63948 Endothelin expression and responsiveness in human ovarian carcinoma cell lines. Moraitis, S.; Langdon, S. P.; Miller, W. R. (Imperial Cancer Research Fund Medical Oncology Unit, Western General Hospital, Edinburgh, EH4 2XU, UK). Eur. J. Cancer, 33(4), 661-668 (English) 1997. CODEN: EJCAEL. ISSN: 0959-8049. Publisher: Elsevier.

AB To elucidate the potential role of endothelins (ETs) as growth regulators in ovarian carcinoma cells in culture, expression of endothelins and their receptors were measured in two **ovarian cancer** cell lines (PEO4 and PEO14), together with the effect of the exogenous addn. of endothelins on the growth of these cell lines in vitro. RT-PCR anal. of mRNA prepd. from PEO4 and PEO14 indicated the presence of ET-1 and ET-3 mRNA. Immunoreactive ET-1-like peptide was found in media from cultures of both PEO4 (1.7 fmol/106 cells/72 h) and PEO14 (20.2 fmol/106 cells/72 h) cell lines. Radioligand binding studies using 125I-ET-1 and membrane fractions were consistent with PEO4 cells having two receptor sites of either high affinity (Kd=0.065 nM, Bmax=0.047 pmol/mg protein) or lower affinity sites (Kd=0.49 nM, Bmax=0.23 pmol/mg protein). Studies using membrane fractions of PEO14 cells indicated that this cell line has only a single lower affinity binding site (Kd=0.56 nM, Bmax=0.31 pmol/mg protein). However, RT-PCR anal. indicated the presence of mRNA from both ETA and ETB receptors in PEO4 and PEO14 cell lines. Exogenous addn. of ETs to PEO4 and PEO14 cells at concns. of 10-10-10-7M resulted in specific dose-dependent increases in cell no. for ET-1 (with max. effects at 10-10 and 10-9M for PEO4 and PEO14, resp.) and ET-2 (max. effects at 20-8 and 10-9M for PEO4 and PEO14, resp.) but not for ET-3. Expts. on the growth of PEO14 cells using BQ123 (ETA-R) antagonist and "antisense" oligonucleotide against the ETA-R, in the absence of exogenous ETs, suggested that immunoreactive ET-1-like material secreted by PEO14 cells can affect their growth in an autocrine manner. These results would be consistent with ET-1 acting as a possible autocrine growth regulator in human ovarian carcinoma cells.

L67 ANSWER 27 OF 50 MEDLINE
97439082 Document Number: 97439082. PubMed ID: 9293534.
Immunohistochemical localization of **endothelin-1**, endothelin-3 and **endothelin receptors** in human pheochromocytoma and paraganglioma. Watanabe K; Hiraki H; Hasegawa H; Tanigawa T; Emura I; Honma K; Shibuya H; Fukuda T; Suzuki T. (Department of Pathology, Fukushima Medical College, Japan.) PATHOLOGY INTERNATIONAL, (1997 Aug) 47 (8) 540-6. Journal code: BXQ; 9431380. ISSN: 1320-5463. Pub. country: Australia. Language: English.

AB Endothelin (ET) and its receptor system have been shown to exert various biological effects on different types of cells in addition to their well-known vasoconstrictor activity. Recently ET-1, ET-3 and the ETB receptor have been shown to play an important role in the development of neural crest-derived cells and, in this context, pheochromocytomas have been reported to harbor ET-1. Endothelin-3 or ET receptor subtypes, however, have not been examined in pheochromocytoma and paraganglioma so far. In the present study the immunohistochemical localization of ET-1/big ET-1, ET-3/big ET-3 and the ETA and ETB receptors were investigated to clarify the biological characteristics of these two tumors using 32 pheochromocytomas and 11 extra-adrenal paragangliomas. **Endothelin -1**/big ET-1 was detected in 19 pheochromocytomas (59%) and eight paragangliomas (72%), while ET-3/big ET-3 was detected in 10 pheochromocytomas (31%) and three paragangliomas (27%). The ETA receptor was found in 21 pheochromocytomas (66%) and in eight paragangliomas (73%), while the ETB receptor was found in 25 pheochromocytomas (78%) and in eight paragangliomas (73%). Normal adrenomedullary cells lacked each antigen examined. Endothelin-immunoreactive tumor cells were distributed focally or in a manner scattered, while receptor-immunostained tumor cells

were distributed with a focal pattern for the ETA receptor and with a focal or diffuse pattern for the ETB receptor. Endothelin and its receptor coexisted in the same tumor in 21 of 28 ET-positive pheochromocytomas and in eight of 10 ET-positive paragangliomas. In addition, seven pheochromocytomas and two paragangliomas revealed positivity of the receptor(s) irrespective of the absence of ET-immunoreactivity. In conclusion, ET and its receptor are frequently and concomitantly expressed in the pheochromocytoma and paraganglioma. From the highly frequent expression of this system or the receptor(s), ET-receptor-mediated signal transduction of these tumors concerning growth and/or cell survival is expected, although definite biological significance of this ligand-receptor system in these tumors awaits further investigation.

L67 ANSWER 28 OF 50 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 10
1997:124332 Document No.: PREV199799430835. In vitro expression of **endothelin-1** (ET-1) and the ETA-A and ET-B ET receptors by the prostatic epithelium and stroma. Grant, Ewan S. (1); Brown, Tom; Roach, Alan; Williams, Brent C.; Habib, Fouad K.. (1) Univ. Dep. Surg., Western Gen. Hosp., Crewe Rd. S., Edinburgh EH4 2XU UK. Journal of Clinical Endocrinology & Metabolism, (1997) Vol. 82, No. 2, pp. 508-513. ISSN: 0021-972X. Language: English.

AB RT-PCR analysis of total RNA prepared from the **prostate cancer** cell lines DU145 and PC3 and from primary epithelial cells indicated the presence of **endothelin-1** (ET-1) messenger RNA (mRNA). Neither the LNCaP cell line nor primary prostatic stromal cells possess ET-1 mRNA transcripts. Seventy-two-hour-conditioned media derived from DU145, PC3, and primary epithelia contain immunoreactive ET concentrations equivalent to 0.814 +- 0.048, 0.330 +- 0.050, and 0.856 +- 0.055 fmol/mL/10-6 cells after 72 h, respectively. Basal immunoreactive ET secretion was exhibited by LNCaP (0.029 +- 0.009 fmol/10-6 cells after 72 h) and stromal cells (0.067 +- 0.007 fmol/mL/10-6 cells after 72 h). Examination of ET-A and ET-B gene expression by RT-PCR demonstrates that ET receptor mRNA is almost completely undetectable in the **prostate cancer** cell lines. Both ET-A and ET-B mRNAs are detectable in primary cultures of prostatic epithelia and stroma. Competitive binding studies demonstrate a single class of binding site in both primary benign epithelia (dissociation constant = 1.85 times 10-10 mol/L; maximal binding capacity = 2.7 times 10-4 binding sitecell), and stroma (dissociation constant = 1.93 times 10-10 mol/L; maximal binding capacity = 3.7 times 10-5 binding sites/cell). Use of selective ET receptor antagonists confirmed that the predominant stromal receptor subtype expressed in vitro is ET-B. This receptor seems not to be coupled to mitogenic pathways because no growth response to exogenous ET-1 or cooperation between ET-1 and bFGF could be observed. Similarly, no effect of ET-1 or the ET-converting enzyme inhibitor, phosphoramidon, on benign epithelial cells could be observed over a 4-day period.

L67 ANSWER 29 OF 50 CAPLUS COPYRIGHT 2001 ACS
1997:586086 Document No. 127:230008 The role of **endothelin-1** in epidermal hyperpigmentation and signaling mechanisms of mitogenesis and melanogenesis. Imokawa, G.; Kobayashi, T.; Miyagishi, M.; Higashi, K.; Yada, Y. (Biological Science Laboratories, Kao Corporation, Haga, 321-34, Japan). Pigm. Cell Res., 10(4), 218-228 (English) 1997. CODEN: PCREEA. ISSN: 0893-5785. Publisher: Munksgaard.

AB The paracrine linkage of endothelins (ET) between keratinocytes and melanocytes suggested that ETs are intrinsic mediators for human melanocytes in UVB-induced pigmentation. In this study, the role of ET-1 in the epidermal hyperpigmentation was investigated in vivo and in vitro. The addn. of 10 nM ET-1 induced a H-7 (10 .mu.M) suppressible-increase in tyrosinase activity in cultured human melanocytes and was accompanied by elevated levels of tyrosinase and tyrosinase-related protein-1 mRNA expression as shown by Northern blotting. Anal. of signaling mechanisms

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leading to tyrosinase activation demonstrated the involvements of quick translocation of PKC, the H-7 (10 .mu.M) suppressible-phosphorylation of the threonine residue of several proteins, and highly elevated level of cAMP (4-fold over control). Reverse transcription polymerase chain reaction (RT-PCR) of RNA isolated from the epidermis of human skin exposed to UVB revealed that UVB irradn. with a dose of 2 MED caused a significant increase in the expressions of ET-1, IL-1.alpha., and tyrosinase mRNA signals 5 days after irradn. The involvement of ET-1 in UVB-pigmentation was also corroborated by the expts. that the exts. of M. Chamomilla, which can act as an antagónist for ET-receptor binding-mediated signaling but has no inhibitory effect on tyrosinase activity in culture, had a significant inhibitory effect on UVB-induced pigmentation in vivo when daily applied immediately after UVB exposure to human skin. These findings suggest that ET-1 is an important mediator in the epidermis for UVB-induced pigmentation in vivo.

L67 ANSWER 30 OF 50 CAPLUS COPYRIGHT 2001 ACS

1997:302266 Document No. 126:304367 Regular immunohistochemical localization of **endothelin-1** and endothelin-B receptor in normal, hyperplastic and neoplastic human adrenocortical cells. Hiraki, Hiroyuki; Hoshi, Nobuo; Hasegawa, Hiroshi; Tanigawa, Toshitaka; Emura, Iwao; Seito, Tsutomu; Yamaki, Toshifumi; Fukuda, Takeaki; Watanabe, Kazuo; Suzuki, Toshimítsu (Department of Pathology, Fukushima Medical College, Fukushima, 960-12, Japan). Pathol. Int., 47(2/3), 117-125 (English) 1997. CODEN: PITEES. ISSN: 1320-5463. Publisher: Blackwell.

AB The localization of endothelin (ET)-1/big ET-1, ET-3/big ET-3, ET-A and ET-B receptor was immunohistochem. examd. in human adrenal glands composed of 36 normal cases, nine hyperplasia, 70 adenomas and seven carcinomas of cortical cells. In normal adrenals, ET-1/big ET-1 and ET-B receptor were regularly detected in the cortical cells, esp. in the zona fasciculata for ET-1 and zona glomerulosa for ET-B receptor but not in the medulla, while ET-A receptor localized occasionally in endothelial cells or rarely in cortical cells and ET-3/big ET-3 was very limited in the cortical cells. In hyperplasia, adenoma and carcinoma, ET-1/big ET-1 and ET-B receptor showed frequent localization, although focal distribution of the ET-B receptor was rather predominant in these groups. ET-A receptor and ET-3/big ET-3 were very infrequently expressed. Functioning vs. non-functioning and hypertensive vs. normotensive cases revealed no significant differences in the frequency of pos. cells for ET-1/big ET-1, ET-3/big ET-3, ET-A receptor or ET-B receptor. Alternatively, the frequency of immunoreactivity to ET-1/big ET-1 or ET-B receptor significantly decreased in hyperplasia, adenoma and carcinoma, when compared with that of normal adrenal cortex. The present study, therefore, indicates that ET-1/big ET-1 and ET-B receptor are a prevalent ligand-receptor system in normal and hyperplastic/neoplastic adrenocortical cells, even with a malignant profile, and may contribute in maintaining adrenocortical cell function or cell viability but not cell growth or systemic hypertension.

L67 ANSWER 31 OF 50 CAPLUS COPYRIGHT 2001 ACS

1996:604434 Document No. 125:297502 The **endothelin receptors** that mediate aggregation of pigment in fish melanophores. Hayashi, Hiroshi; Nakamura, Satoshi; Fujii, Ryozo (Department Biomolecular Science, Toho University, Chiba, 274, Japan). Comp. Biochem. Physiol., B: Biochem. Mol. Biol., 115B(1), 143-152 (English) 1996. CODEN: CBPBB8. ISSN: 0305-0491.

AB A study was made of effects on the melanophores of several teleosts of 3 isopeptides of mammalian endothelin (ET), namely, ET-1, ET-2, and ET-3. In all the species examd., these peptides induced the aggregation of pigment within the melanophores. Chem. denervated melanophores also responded to ETs quite normally. Thus, ETs may act directly on the cells. Quant. studies on the dark chub and zebrafish indicated that the response

was concn. dependent, and that the 3 peptides were almost equipotent. Sarafotoxin S6c, a specific agonist of the mammalian ETB receptor, also effectively induced the aggregation of pigment in a concn.-dependent manner. IRL 1620, another specific agonist of the ETB receptor, also induced the aggregation of pigment, but only at higher doses. BQ-123 and TTA-386, potent selective antagonists that bind to mammalian receptor of the ETA type, did not interfere with the pigment-aggregating actions of ETs, whereas BQ-788, an ETB receptor-selective antagonist, strongly inhibited the action of ETs. It appears, therefore that the receptors for ET that mediate the aggregation of pigment in fish melanophores resemble those of the mammalian ETB type.

L67 ANSWER 32 OF 50 CAPLUS COPYRIGHT 2001 ACS
1996:598188 Document No. 125:244458 Decrease in ETB receptor in cultured human metastatic **melanoma** cells. Kikuchi, Kanako; Kadono, Takafumi; Etoh, Takafumi; Nakagawa, Hidemi; Tamaki, Kunihiko (Branch Hospital, Tokyo University, Tokyo, 112, Japan). Int. Congr. Ser., 1096(Melanogenesis and Malignant Melanoma: Biochemistry, Cell Biology, Molecular Biology, Pathophysiology, Diagnosis and Treatment), 77-85 (English) 1996. CODEN: EXMDA4. ISSN: 0531-5131.
AB In this study, the authors examd. the endothelin (ET) receptor subtype involved in mitogenic signaling in human primary and metastatic **melanoma**. In a reverse transcriptase-polymerase chain reaction (RT-PCR) study, ETB mRNA expression in metastatic **melanoma** cells was decreased compared to primary **melanoma**. Only RPM-EP, a primary recurrent **melanoma** cell line, showed strong ETA mRNA expression. ET-1 and ET-3 stimulated DNA synthesis of primary and recurrent cutaneous **melanoma** cells in serum-deprived cultures. The growth response to ET-1 in metastatic **melanoma** cells was decreased compared to primary **melanoma** cells. [125I]-IRL-1620 binding to PM-WK, a primary **melanoma** cell line, was significantly blocked by excessive amts. of unlabeled BQ-788. [125I]-IRL-1620 binding to metastatic **melanoma** cells was significantly decreased compared to primary **melanoma** cells. From these results, the authors conclude that the mitogenic effects of ET in human primary **melanoma** are mainly mediated through ETB receptors and that down-regulation of ETB receptors causes the decreased growth response of ET-1 in metastatic **melanoma** cells.

L67 ANSWER 33 OF 50 MEDLINE DUPLICATE 11
96013664 Document Number: 96013664. PubMed ID: 7560095. Expression and localization of **endothelin-1** and **endothelin receptors** in human meningiomas. Evidence for a role in tumoral growth. Pagotto U; Arzberger T; Hopfner U; Sauer J; Renner U; Newton C J; Lange M; Uhl E; Weindl A; Stalla G K. (Max-Planck Institute of Psychiatry, Clinical Institute, Munich, Germany.) JOURNAL OF CLINICAL INVESTIGATION, (1995 Oct) 96 (4) 2017-25. Journal code: HS7; 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.
AB In addition to its well-known homoeostatic actions in the cardiovascular system, ET-1 has been shown to constitute a potent growth regulatory peptide in various tissues. We have studied the expression of ET-1 and its receptors (ET-Ar and ET-Br) in human meningiomas (n = 35) as well as their involvement in cellular growth. By PCR of reverse-transcribed RNA we detected ET-1 mRNA in 91% (32 of 35), ET-Ar mRNA in 82% (29 of 35), and ET-Br mRNA in 42% (15 of 35) of human meningiomas examined. The localization of ET-1 mRNA, ET-Ar mRNA, and ET-1 peptide in tumoral cells was observed by in situ hybridization and immunohistochemistry, whereas ET-Br mRNA was expressed at low level only in cells belonging to blood vessels. In addition, we found that ET-1 stimulated [3H] thymidine incorporation in primary cell cultures of 20 meningiomas and that this effect could be blocked by BQ-123, a specific antagonist for ET-Ar. In contrast, RES-701-3, an antagonist of ET-Br, did not block the

proliferative effect of ET-1. In conclusion, our data provide evidence that ET-1 constitutes an important growth factor for meningiomas acting via ET-Ar. We can hypothesize that ET-1, acting in concert with other growth factors and cytokines, is involved in the meningioma tumorigenesis.

L67 ANSWER 34 OF 50 CAPLUS COPYRIGHT 2001 ACS
1995:701681 Document No. 123:103442 Endothelin receptor in human astrocytoma U373MG cells: binding, dissociation, receptor internalization. Wu-Wong, Jinshyun R.; Chiou, William J.; Magnuson, Scott R.; Opgenorth, Terry J. (Pharm. Products Div., Abbott Lab., Abbott Park, IL, USA). J. Pharmacol. Exp. Ther., 274(1), 499-507 (English) 1995. CODEN: JPETAB. ISSN: 0022-3565.

AB Endothelin (ET) receptor in human astrocytoma U373MG cells was characterized. ET-1, ET-3, sarafotoxin S6C, IRL1620, BQ788, Ro46-2005 and PD142893 inhibited specific [125I]ET-1 binding with Ki values of 0.03 0.06, 0.74, 5.01, 4.45, 2275 and 157 nM, resp. ETA selective antagonists BQ123 and FR139317 at 1 .mu.M did not block [125I]ET-1 binding. Reverse transcription-polymerase chain reaction confirmed the results from competition studies that U373 cells expressed predominantly ETB receptor. The Bmax and KD values of [125I]ET-1 binding were 0.15 pmol/1 .times. 106 cells and 0.23 nM. The mol. mass for the receptor was 45 kDa. ET-1 binding did not stimulate Ca2+ mobilization, phosphatidylinositol hydrolysis or arachidonic acid release, nor did it affect the intracellular cAMP or cGMP level. Interestingly, a majority of ET (>80%) bound to the receptor was rapidly internalized, consistent with emerging evidence that a major function of ETB receptor is to clear ET. [125I]ET-1 binding was time-dependent and bound [125I]ET-1 was difficult to dissoc. In contrast, bound antagonists were much easier to dissoc. The results suggest that agonists and antagonists of the ET receptor exhibited different dissocn. characteristics, with antagonist binding more reversible than agonist binding.

L67 ANSWER 35 OF 50 CAPLUS COPYRIGHT 2001 ACS
1995:966287 Document No. 124:1534 Characterization of **endothelin receptors** in human brain cortex, gliomas, and meningiomas. Harland, Spencer P.; Kuc, Rhoda E.; Pickard, John D.; Davenport, Anthony P. (Clinical Pharmacology Unit, Univ. of Cambridge, Cambridge, UK). J. Cardiovasc. Pharmacol., 26(Suppl. 3), S408-S411 (English) 1995. CODEN: JCPCDT. ISSN: 0160-2446.

AB The authors have characterized the endothelin (ET) receptor subtypes present within normal human cerebral cortex (CC), glioblastoma multiforme (GBM), and meningiomas (MGs), using 2 subtype-selective radioligands, [125I]-PD 151242 (ETA) and [125I]-BQ 3020 (ETB). For satn. expts., sections of tissue were incubated with increasing concns. (8 pM-4 nM) of either [125I]-PD 151242 or [125I]-BQ 3020 in incubation and buffer (22.degree., 2 h). In satn. binding assays, [125I]-PD 151242 bound with high affinity to a single population of ET receptors (n = individuals) in normal CC (Kd 1.23 nM; Bmax 28.10 fmol/mg protein), GBM (Kd 1.62 nM; Bmax 147.04 fmol/mg protein), and MGs (Kd 3.10 nM; Bmax 290.3 fmol/mg protein). [125I]-BQ 3020 also bound with high affinity to a single population of ET receptors in normal CC (Kd 4.54 nM; Bmax 190.5 fmol/mg protein), GBM (Kd 1.38 nM; Bmax 234.0 fmol/mg protein), and MGs (Kd 0.25 nM; Bmax 22.8 fmol/mg protein). To det. receptor subtype localization, autoradiog. was performed after incubation of sections with 0.1 nM [125I]-ET-1 (ETA and ETB), [125I]-PD 151242 (ETA), and [125I]-BQ 3020 (ETB). Autoradiog. demonstrated a high concn. of ETA receptors within the pial and intraparenchymal vessels and meninges overlying the CC. Gray and white matter were diffusely ETB-pos. GBM had a strongly vascular pattern of ETA distribution. ETA receptors were dense and homogeneous in MGs. [125I]-PD 151242 binds with high affinity to human pial and intraparenchymal vessels and is able to clearly delineate the microvasculature in GBM. Selective ETA receptor manipulation may have potential benefits in cerebrovascular

disease and neoplasia without producing detrimental effects on the predominantly ETB-pos. brain parenchyma.

L67 ANSWER 36 OF 50 CAPLUS COPYRIGHT 2001 ACS
1995:724445 Document No. 123:140462 Endothelin receptor in microvessels isolated from human meningiomas: quantification with radioluminography. Yamaga, Sei-ichi; Tsutsumi, Keisuke; Niwa, Masami; Kitagawa, Naoki; Anda, Takeo; Himeno, Akihiko; Khalid, Humayun; Taniyama, Kohtaro; Shibata, Shobu (School of Medicine, Nagasaki University, Nagasaki, 852, Japan). Cell. Mol. Neurobiol., 15(3), 327-40 (English) 1995. CODEN: CMNEDI. ISSN: 0272-4340.

AB The authors characterized specific 125I-**endothelin-1** (125I-ET-1) binding sites in microvessels isolated from human meningiomas, using an in vitro quant. receptor autoradiog. technique coupled to a radioluminog. imaging plate system. This newly developed and highly sensitive method revealed high-affinity ET receptors present in pellet sections of the microvessels from all the meningiomas studied, regardless of histol. subtypes (dissocn. const., 1.2 nM; max. binding capacity, 185 fmol/mg; for 9 tumors). In 5 cases of meningiomas, ET-3 competed for 125I-ET-1 binding to microvessels from those tumors with a low affinity [50% inhibiting concn. (IC50) of 1.6.times.10-6M], and a selective ETB receptor agonist, sarafotoxin S6c, up to 10-6M, did not displace ET binding from the sections. In the sections of microvessels from 4 other tumors, biphasic competition curves were obtained in the case of incubation in the presence of increasing concns. of ET-3, with an IC50 of 1.1.times.10-9M for the high-affinity component and 1.6.times.10-6M for the low-affinity component, resp. In addn., S6c competed for ET binding to those sections (IC50 = 2.3.times.10-10M) and 10-6M S6c displaced 30% of the control, corresponding to the high-affinity component of competition curves obtained in the presence of ET-3. Apparently, (1) capillaries in human meningiomas express a large no. of high-affinity ETA (non-ETB) receptors with a small proportion of ETB receptors, and (2) ET may have a role in neovascularization, tumor blood flow, and(or) function of the blood-tumor barrier in meningioma tissues by interacting with specific receptors present on the surface of the endothelium.

L67 ANSWER 37 OF 50 MEDLINE DUPLICATE 12
95118808 Document Number: 95118808. PubMed ID: 7819049. Decreased expression of messenger RNAs encoding **endothelin receptors** and neutral endopeptidase 24.11 in endometrial **cancer**. Pekonen F; Nyman T; Ammala M; Rutanen E M. (Minerva Institute for Medical Research, Helsinki.) BRITISH JOURNAL OF CANCER, (1995 Jan) 71 (1) 59-63. Journal code: AV4; 0370635. ISSN: 0007-0920. Pub. country: SCOTLAND: United Kingdom. Language: English.

AB In this study, we used reverse transcriptase-polymerase chain reaction (RT-PCR) to compare the expression of mRNAs encoding **endothelin-1** (ET-1), **endothelin receptors** type A (ETA-R) and type B (**ETB**-R) and ET-1-degrading enzyme neutral endopeptidase 24.11 (NEP) in 15 endometrial **cancer** tissues and 13 normal endometrial tissues. The relative levels of ET-1 mRNA in endometrial **cancer** tissues did not differ from those in normal endometrium. Both ETA-R and **ETB**-R mRNA levels were significantly lower in endometrial **cancer** tissue than in normal endometrium ($P < 0.001$). The complete lack of NEP mRNA in endometrial **cancer** tissues was in marked contrast to results from normal endometrium ($P < 0.001$). In conclusion, differential expression of mRNAs encoding ET-R and NEP in normal endometrium and endometrial **cancer** suggests that ET action is altered in endometrial **cancer** compared with normal endometrium.

L67 ANSWER 38 OF 50 CAPLUS COPYRIGHT 2001 ACS
1995:352450 Document No. 122:152200 [3H]BQ-123, a highly specific and

reversible radioligand for the endothelin ETA receptor subtype. Ihara, Masaki; Yamanaka, Rie; Ohwaki, Kenji; Ozaki, Satoshi; Fukami, Takehiro; Ishikawa, Kiyofumi; Towers, Pat; Yano, Mitsuo (Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Okubo 3, Tsukuba, 300-33, Japan). Eur. J. Pharmacol., 274(1-3), 1-6 (English) 1995. CODEN: EJPHAZ. ISSN: 0014-2999.

AB The mode of binding of [3H]BQ-123 (cyclo(-D-Trp-D-Asp-[prolyl-3,4(n)-[3H]]Pro-D-Val-Leu-)), an **endothelin receptor** antagonist radioligand, was evaluated in the human neuroblastoma cell line SK-N-MC at 37.degree.. Scatchard anal. indicated the presence of a single class of [3H]BQ-123 binding sites with a high affinity of 3.2 nM. [3H]BQ-123 binding achieved steady state within 7 min and dissocd. with a half-time of 1.4 min, while [125I]**endothelin-1** binding barely reached a steady state even after 6 h and showed little dissocn. [3H]BQ-123 binding was sensitive to **endothelin-1** and endothelin-2 (Ki values = 0.058 and 0.10 nM, resp.) and the endothelin ETA receptor-selective antagonist BQ-123 (Ki = 3.3 nM), while showing low affinity for endothelin-3 (Ki = 50 nM), the endothelin **ETB** receptor-selective agonist BQ-3020 (Ki = 970 nM) and other bioactive peptides. Thus, [3H]BQ-123 is a specific and reversible radioligand for endothelin ETA receptors. The rapid reversibility of [3H]BQ-123 binding should provide a tool for estg. the equil. inhibition consts. (Ki values) of various compds. for endothelin ETA receptors.

L67 ANSWER 39 OF 50 CAPLUS COPYRIGHT 2001 ACS

1994:571391 Document No. 121:171391 Gene expression, localization, and characterization of endothelin A and B receptors in the human adrenal cortex. Rossi, GianPaolo; Albertin, Giovanna; Belloni, Anna; Zanin, Lucia; Biasolo, Maria Angela; Prayer-Galetti, Tommaso; Bader, Michael; Nussdorfer, Gastone G.; Palu, Giorgio; Pessina, Achille C. (Dep. Clin. Med., Univ. Padova, Italy). J. Clin. Invest., 94(3), 1226-34 (English) 1994. CODEN: JCINAO. ISSN: 0021-9738.

AB Compelling evidence indicates that the endothelium-derived potent vasoconstrictor **endothelin-1** (ET-1) stimulates aldosterone secretion by interacting with specific receptors. Although two different ET-1 receptors have been identified and cloned, the receptor subtype involved in mediating aldosterone secretion is still unknown. Accordingly, the authors wished to investigate whether the genes of ET-1 and of its receptors A and B are expressed in the normal human adrenal cortex. The authors designed specific primers for ET-1 and the ETA and ETB receptors genes and developed a reverse transcription polymerase chain reaction (RT-PCR) with chemiluminescent quantitation of the cDNA. In addn., the authors carried out 125I ET-1 displacement studies with cold ET-1, ET-3 and the specific ETA and ETB ligands BQ 123 and sarafotoxin 6C. Localization of each receptor subtype was also investigated by autoradiog. Binding expts. were first individually analyzed by Scatchard and Hofstee plot and then coanalyzed by the nonlinear iterative curve fitting program Ligand. Histol. normal adrenal cortex tissue, obtained from kidney **cancer** patients, and an aldosterone-producing adenoma (APA), which is histogenetically derived from the zona glomerulosa (ZG) cells, were studied. Results showed that the ET-1, ETA and ETB mRNA can be detected by RT-PCR in all adrenal cortices as well as in the APA. The best fitting of the 125I ET-1 displacement binding data was consistently provided by a two-site model both in the normal adrenal cortex (F = 22.1) and in the APA (F = 18.4). In the former the d. (Bmax) of the ETA and ETB subtype was 2.6 pmol/mg protein and 1.19, resp. The dissocn. const. (Kd) of ET-1, ET-3, S6C, and BQ 123 for each receptor subtype was within the range reported for human tissue for the ETA and ETB receptors. In the APA tissue, the Bmax tended to be lower (1.33 and 0.8 pmol/mg protein, for the ETA and ETB, resp.) but the Kd were similar. Autoradiog. studies confirmed the presence of both receptor subtypes on the ZG as well as on APA cells. Thus, the genes of ET-1 and both its receptor subtypes ETA and

ETB are actively transcribed in the human adrenal cortex. Furthermore, both receptor subtypes are translated into proteins in ZG and APA cells.

L67 ANSWER 40 OF 50 MEDLINE DUPLICATE 13
94142056 Document Number: 94142056. PubMed ID: 8309002. Localization of **endothelin receptors** in the human prostate. Kobayashi S; Tang R; Wang B; Opgenorth T; Stein E; Shapiro E; Lepor H. (Department of Urology, Medical College of Wisconsin, Milwaukee.) JOURNAL OF UROLOGY, (1994 Mar) 151 (3) 763-6. Journal code: KC7; 0376374. ISSN: 0022-5347. Pub. country: United States. Language: English.
AB The objective of the present study was to localize **endothelin receptors** in the human prostate using quantitative autoradiography. Slide-mounted tissue sections 20 microns. in thickness were obtained from the transition zones of seven patients undergoing radical prostatectomies for low volume **prostate cancer** . Sarafotoxin (S6C) and BQ123 have been used to distinguish **endothelin receptor** subtypes (ETA and **ETB**). The prostatic tissue sections were incubated in four different stock solutions containing the following: 0.1 nM. 125I-**endothelin-1** (125I-ET-1) (total ET-1 binding); 0.1 nM. 125I-ET-1 and 100 nM. S6C (total ETA binding); 0.1 nM. 125I-ET-1 and 1 microM. BQ123 (total **ETB** binding); and 0.1 nM. 125I-ET-1 and 1 microM. ET-1 (nonspecific ET-1 binding). Nonspecific binding accounted for only 12 and 15% of total 125I-ET-1 binding in the stroma and glandular epithelium. Autoradiograms were quantitatively analyzed using a computerized image analysis system. Specific radioactive densities (nCi/mg.) were determined for the stromal and glandular epithelial elements of the prostate. The specific radioactive densities of ETA and **ETB** binding sites in the stroma were 7.57 +/- 0.65 and 2.98 +/- 0.81. The specific radioactive densities of ETA and **ETB** binding sites in the glandular epithelium were 1.59 +/- 0.15 and 7.87 +/- 1.35. The present study demonstrates that the predominant **endothelin receptors** in the stroma and glandular epithelium are the ETA and **ETB** subtypes, respectively.

L67 ANSWER 41 OF 50 CAPLUS COPYRIGHT 2001 ACS
1994:401975 Document No. 121:1975 The receptors for endothelins and their analogs in SK-N-MC neuroblastoma cells. Huggins, John P.; Pelton, John T.; van Giersbergen, Paul L. M. (Marion Merrell Dow Res. Inst., Strasbourg, F-67000, Fr.). Peptides (Tarrytown, N. Y.), 15(3), 529-36 (English) 1994. CODEN: PPTDD5. ISSN: 0196-9781.
AB The potency order of peptides to inhibit [125I]**endothelin-1** binding and to stimulate phosphatidylinositol phosphate (PtdInsP) turnover in SK-N-MC cells was consistent with the presence of ETA-**endothelin receptors**. Divalent cations enhanced [125I]**endothelin-1** binding by, in the case of Mn2+, increasing radioligand affinity. Mn2+ did not induce conformational changes in **endothelin-1**, and its effect was maintained in solubilized receptors. Hence, metal ions may directly interact with **endothelin receptors**. The effects of BQ-123 and [Ala1,3,11,15]**endothelin-1** on PtdInsP turnover were investigated. Concn.-response curves of endothelins were modeled by a second-order equation that assumes pseudo-irreversible ligand binding.

L67 ANSWER 42 OF 50 MEDLINE DUPLICATE 14
95026828 Document Number: 95026828. PubMed ID: 7524189. Endothelin receptor density in human hypertrophic and non-hypertrophic prostate tissue. Kondo S; Morita T; Tashima Y. (Second Department of Biochemistry Akita University, School of Medicine.) TOHOKU JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Apr) 172 (4) 381-4. Journal code: VTF; 0417355. ISSN: 0040-8727. Pub. country: Japan. Language: English.
AB The amount of **endothelin receptors** in human prostate

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tissue was measured by radioligand binding techniques using 125I-**Endothelin** -1 and -3 (125I-ET-1, -3). Specimens of the non-hypertrophy group were obtained from 6 patients who underwent total cystectomy under the diagnosis of bladder **cancer** and those of the hypertrophy group from 6 prostatic hypertrophy patients who underwent open prostatectomy. 125I-ET-1 bound to the prostate tissue with the KD value of 0.033 +/- 0.012 nM in the non-hypertrophy group and with the KD value of 0.035 +/- 0.012 nM in the hypertrophy group. 125I-ET-3 bound to the prostate tissue with the KD value of 0.023 +/- 0.011 nM in the non-hypertrophy group and with the KD value of 0.029 +/- 0.016 nM in the hypertrophy group. The KD values were not significantly different between the hypertrophy and non-hypertrophy groups. The KD values of 125I-ET-1 and 125I-ET-3 were similar. The Bmax values (fmol/mg protein) of 125I-ET-1 binding to the prostate tissue were 32.18 +/- 3.69 to the non-hypertrophy group and 85.66 +/- 20.65 to the hypertrophy group. The Bmax values (fmol/mg protein) of 125I-ET-3 binding to the prostate tissue were 27.48 +/- 5.25 to the non-hypertrophy group and 75.90 +/- 13.46 to the hypertrophy group. The Bmax values of both 125I-ET-1 and 125I-ET-3 were significantly higher in the hypertrophy group than in the non-hypertrophy group.(ABSTRACT TRUNCATED AT 250 WORDS)

L67 ANSWER 43 OF 50 CAPLUS COPYRIGHT 2001 ACS
1995:17243 Document No. 122:123817 **Endothelin receptors** in the human urinary bladder are different from those in the human ureter. Takeda, M.; Komeyama, T.; Koizumi, T.; Hatano, A.; Tamaki, M.; Takahashi, H.; Tsutsui, T.; Mizusawa, T.; Obara, K. (Sch. Med., Niigata Univ., Niigata, 951, Japan). Clin. Invest., 72(3), 213 (English) 1994. CODEN: CINVE8. ISSN: 0941-0198.
AB Human urinary bladders from cystectomy for bladder **cancer** and human ureters from nephrectomy for renal cell **cancer** were used for isometric contraction expts. Cumulative conc.-response curves to **endothelin-1** (I) and sarafotoxin S6C (II) were constructed. I produced concn.-dependent contractions of the human urinary bladder, whereas II produced only little contraction. Both I and II produced concn.-dependent contraction of the human ureter.

L67 ANSWER 44 OF 50 CAPLUS COPYRIGHT 2001 ACS
1993:643793 Document No. 119:243793 Cloning and characterization of an endothelin-3 specific receptor (ETC receptor) from Xenopus laevis dermal melanophores. Karne, Suresh; Jayawickreme, Channa K.; Lerner, Michael R. (Sch. Med., Yale Univ., New Haven, CT, 06510, USA). J. Biol. Chem., 268(25), 19126-33 (English) 1993. CODEN: JBCHA3. ISSN: 0021-9258.
AB The authors report here the presence of a receptor specific for endothelin-3 (termed ETC receptor or ETCR) on Xenopus laevis dermal melanophores. Activation of ETCR causes the dispersion of the pigment granules within the melanophores. The EC50 for ET-3 to induce the pigment dispersion is 24 .+-. 7 nM, compared to greater than 10 .mu.M for both ET-1 and -2. This effect desensitizes in a manner that is dependent on both time and the concn. of ET-3 used to stimulate the cells. A cDNA encoding for ETCR was isolated by a polymerase chain reaction-mediated DNA amplification strategy using degenerate oligonucleotides prepd. based on conserved regions of other known G-protein-coupled receptor sequences and by the subsequent screening of a frog melanophore cDNA library. The cloned cDNA consists of 2,240 nucleotides, with an open reading frame coding for 444 amino acids contg. an initial 20-amino acid signal sequence. The predicted mature peptide consists of 424 amino acids with a heptahelical structure common to the G-protein-coupled receptor superfamily. Its deduced amino acid sequence is 47 and 52% identical to ETA and **ETB** receptors, resp., while ETA and **ETB** are 48% identical to each other. Expression of cDNA in HeLa cells, which do not contain **endothelin receptors**, enables the cells to specifically bind[125I]ET-3. Competition binding expts. performed on HeLa

cells transiently expressing pETC show that the apparent Ki values for ET-3 and ET-1 to displace [125I]ET-3 are 45.5.+-. 16 and 114 .+-. 22 nM, resp.

L67 ANSWER 45 OF 50 MEDLINE DUPLICATE 15
93373240 Document Number: 93373240. PubMed ID: 8364873. Impaired binding properties of **endothelin-1** receptors in human endometrial carcinoma tissue. Ben-Baruch G; Schiff E; Galron R; Menczer J; Sokolovsky M. (Department of Obstetrics and Gynecology, Sheba Medical Center, Sackler School of Medicine, Tel-Hashomer, Israel.) CANCER, (1993 Sep 15) 72 (6) 1955-8. Journal code: CLZ; 0374236. ISSN: 0008-543X. Pub. country: United States. Language: English.
AB BACKGROUND. Endothelins, potent stimulators of smooth muscle tissue activity, were recently shown to also function as mitogens for numerous cell types. The authors investigated the properties of **endothelin -1** (ET-1) receptors in human endometrial tissue compared with human endometrial carcinoma tissue. METHODS. Tissue samples from 13 patients with endometrial carcinoma and from 12 women undergoing hysterectomy due to uterus myomatous were obtained immediately after surgical removal. Binding properties of the **endothelin receptors** were studied using 125I-labeled ET-1. RESULTS. A significant difference was demonstrated between binding properties of ET-1 receptors of these two groups. The mean maximal density (Bmax) value of the normal endometrial samples was 2029 +/- 341 fmol/mg protein, whereas that of the neoplastic samples was 356 +/- 121 fmol/mg protein. No differences were found, however, between the mean dissociation constant (Kd) values of these groups. CONCLUSIONS. These results might be compatible with the increased blood flow that characterizes malignant endometrial tissue. However, they do not indicate an important mitogenic role for ET-1 in the development of endometrial **cancer**.

L67 ANSWER 46 OF 50 CAPLUS COPYRIGHT 2001 ACS
1993:74323 Document No. 118:74323 Endothelins stimulate c-fos and nerve growth factor expression in astrocytes and astrocytoma. Ladenheim, R. G.; Lacroix, I.; Foignant-Chaverot, N.; Strosberg, A. D.; Couraud, P. O. (Lab. Immuno-Pharmacol. Mol., Inst. Cochin Genet. Mol., Paris, 75014, Fr.). J. Neurochem., 60(1), 260-6 (English) 1993. CODEN: JONRA9. ISSN: 0022-3042.
AB **Endothelin receptors** have been identified on astrocytes and astrocytoma, but their physiol. significance has remained elusive. It is shown here that endothelins induce c-fos in primary cultures of mouse embryo astrocytes, as well as in two subclones of rat astrocytoma C6 cells, although with different kinetics. In addn., nerve growth factor expression is stimulated, as seen by mRNA accumulation and protein secretion, in primary astrocytes and one of the two C6 subclones, with an apparent correlation with the transience of c-fos induction. The activation of protein kinase C appears as an obligatory step during these processes, because (a) inhibition of protein kinase C by staurosporine blocks the induction by endothelin or phorbol esters of both c-fos and nerve growth factor, and (b) phorbol ester-evoked down-regulation of protein kinase C completely abolishes the c-fos induction by endothelin, but not that by the .beta.-adrenergic agonist isoproterenol, a known activator of the cAMP-dependent pathway. These results support the hypothesis that c-fos product might be implicated in nerve growth factor expression by astrocytes, and also suggest that endothelins may participate in vivo in the modulation of the glial neurotrophic activity during brain development or wound healing.

L67 ANSWER 47 OF 50 CAPLUS COPYRIGHT 2001 ACS
1994:290685 Document No. 120:290685 BQ-123 inhibits both **endothelin 1** and endothelin 3 mediated C6 rat glioma cell proliferation suggesting an atypical endothelin receptor. Sedo, A.; Rovero, P.; Revoltella, R.P.; Di Bartolo, V.; Beffy, P.; Mizrahi, J. (1st Med. Fac.,

Charles Univ., Prague, Czech Rep.). J. Biol. Regul. Homeostatic Agents, 7(3), 95-8 (English) 1993. CODEN: JBRAER. ISSN: 0393-974X.

AB The mitogenic action of endothelins (ETs) 1 and 3 was studied on C6 rat glioma cells in serum-free culture conditions. In order to characterize the ET receptor subtype involved in this effect, BQ-123, an ETA receptor selective antagonist was used. The authors' results confirmed that both ET-1 and ET-3 are mitogenic peptides for C6 cells and demonstrated for the first time that the ETA receptor antagonist BQ-123 inhibits the proliferative effect of both ET-1 and ET-3 in this cellular system, providing evidence of an atypical ET receptor on C6 cells.

L67 ANSWER 48 OF 50 MEDLINE DUPLICATE 16

93118025 Document Number: 93118025. PubMed ID: 1475788. Direct measurement of endothelin receptor in human bladder base and dome using 125I-endothelin. Kondo S; Fushimi E; Morita T; Tashima Y. (Second Department of Biochemistry, Akita University School of Medicine.) TOHOKU JOURNAL OF EXPERIMENTAL MEDICINE, (1992 Jun) 167 (2) 159-61. Journal code: VTF; 0417355. ISSN: 0040-8727. Pub. country: Japan. Language: English.

AB The amount of endothelin receptor in human bladder base and dome was measured by radioligand binding techniques using 125I-**endothelin -1** (125I-ET). Specimens were obtained from 5 patients who underwent total cystectomy under diagnosis of bladder **cancer**. 125I-ET bound to the bladder base with the KD value of 0.004 +/- 0.003 nM and to the bladder dome with the KD value of 0.007 +/- 0.003 nM. These values were not significantly different. The Bmax values (fmol/mg protein) of 125I-ET binding to human bladder were 2.74 +/- 2.81 to the base and 47.3 +/- 9.52 to the dome. There were much larger amount of **endothelin receptors** in the dome compared to the base. The existence of **endothelin receptors** in human bladder suggests the possible roles of endothelin on the human bladder function.

L67 ANSWER 49 OF 50 CAPLUS COPYRIGHT 2001 ACS

1991:507080 Document No. 115:107080 Comparison of endothelin binding and calcium mobilization in C6-BU-1 rat glioma and N18TG2 mouse neuroblastoma cells. Gleason, M. M.; Wu, H. Ling; Yue, T. Li; Feuerstein, G.; Nambi, P. (Dep. Pharmacol., SmithKline Beecham Pharm., King of Prussia, PA, 19406-0939, USA). Neuropeptides (Edinburgh), 19(3), 197-204 (English) 1991. CODEN: NRPPDD. ISSN: 0143-4179.

AB Endothelin (ET) receptor activation increases intracellular calcium concns. ([Ca2+]i) in NG108-15 cells, a hybrid of rat glioma C6-BU-1 and mouse neuroblastoma N18TG2 cells. The origin of the ET receptor and [Ca2+]i mobilization were studied in the parent cell lines hybridized to form the NG109-15 cells. [125I]ET-1 bound to a single class of high-affinity sites in C6-BU-1 cells with a KD value of 108 pM and Bmax of 12,400 sites/cell. ET-1, ET-2, ET-3, and big ET inhibited [125I]ET-1 binding to C6-BU-1 cells with Kd values of 0.074, 0.167, 261, and 187 nM, resp. All ETs produced a rapid increase in [Ca2+]i in C6-Bu-1 cells. EC50 values for ET-1, ET-2, ET-3, and big ET were 0.71, 1.14, 120, and 243 nM, resp. There was a correlation between the Kd values obtained from competition binding expts. and the EC50 values from [Ca2+]i response curves in C6-BU-1 cells. ET-1 at 10 mM produced .apprx.85% of the maximal [Ca2+]i increase in C6-BU-1 cells which was reduced by 96% in the absence of extracellular calcium. Diltiazem (10 .mu.M) and nifedipine (1 .mu.M) failed to block the ET-induced [Ca2+]i mobilization. None of the ETs elevated [Ca2+]i or displayed any specific [125I]ET-1 binding in N18TG2 cells. Thus, ET binds to a specific ET receptor in C6-BU-1 cells and elevates [Ca2+]i through dihydropyridine-insensitive, receptor-mediated calcium influx. The ability of ETs to elevate [Ca2+]i in NG108-15 hybrid cells is due to the ET receptor inherent to the C6-BU-1 glioma parent cell line.

Searched by: Mary Hale 308-4258 CM-1 12D16

L67 ANSWER 50 OF 50 MEDLINE

90349081 Document Number: 90349081. PubMed ID: 2166928. Localization and characterization of **endothelin receptors** in human gliomas: a growth factor?. Kurihara M; Ochi A; Kawaguchi T; Niwa M; Kataoka Y; Mori K. (Department of Neurosurgery, Nagasaki University School of Medicine, Japan.) NEUROSURGERY, (1990 Aug) 27 (2) 275-81. Journal code: NZL; 7802914. ISSN: 0148-396X. Pub. country: United States. Language: English.

AB Localization and characterization of **endothelin receptors** in surgical specimens of human gliomas (6 benign astrocytomas and 7 glioblastomas multiforme) and in normal human cortices were studied using quantitative receptor autoradiographic methods. Low numbers of [125I]**endothelin-1** [(125I]ET-1) binding sites were detected in the gray matter of the human frontal cortex, with little binding in the white matter. Conversely, relatively high numbers of [125I]ET-1 binding sites were homogeneously present in tissue sections derived from astrocytomas, whereas higher numbers of [125I]ET-1 binding sites were heterogeneously located on groups of cells with a pseudopalisading appearance and pleomorphic astrocytes in glioblastoma multiforme. Necrotic areas within the tissue sections derived from glioblastoma were devoid of binding. Binding of [125I]ET-1 to gliomas and normal gray matter was specific. Unlabeled ET-1 and its natural analogs (ET-2 and ET-3) inhibited the binding of [125I]ET-1 to these lesions in a concentration-dependent manner and with similar high potencies. Possibly related substances, such as ion channel regulators (omega-conotoxin, apamin, and tetrodotoxin), a Ca2+ channel blocker (nicardipine), and growth factors (epidermal growth factor and insulin-like growth factor I), did not affect the binding to tissue sections derived from gliomas or from normal frontal cortices. Scatchard analysis revealed the presence of a single class and high-affinity binding sites for endothelin in normal cortex and in gliomas. There was no significant difference in the binding affinities: dissociation constants (Kd) were 2.1 +/- 0.5 nM in 6 astrocytomas, 2.5 +/- 0.4 nM in 7 glioblastomas, and 1.4 and 1.5 nM in two normal cortices.(ABSTRACT TRUNCATED AT 250 WORDS)

'IN' IS NOT A VALID FIELD CODE
L68 1315 FILE MEDLINE
L69 1451 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L70 201 FILE BIOTECHNO
L71 1900 FILE CAPLUS
'IN' IS NOT A VALID FIELD CODE
L72 916 FILE EMBASE
L73 8 FILE JICST-EPLUS
L74 880 FILE WPIDS

TOTAL FOR ALL FILES
L75 6671 SCHNEIDER, R?/AU,IN OR SCHNEIDER R?/AU,IN

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L80 48 FILE EMBASE
L81 7 FILE JICST-EPLUS
L82 1 FILE WPIDS

Searched by: Mary Hale 308-4258 CM-1 12D16

TOTAL FOR ALL FILES
L83 246 JAMAL, S?/AU,IN OR JAMAL S?/AU,IN

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L84 0 FILE MEDLINE
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L86 0 FILE BIOTECHNO
L87 1 FILE CAPLUS
L88 0 FILE EMBASE
L89 0 FILE JICST-EPLUS
L90 1 FILE WPIDS

TOTAL FOR ALL FILES
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L92 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
2000:790734 Document No. 133:329575 Cancer treatment with endothelin receptor antagonists. **Schneider, Robert J.**; Jamal, Sumayah (New York University, USA). PCT Int. Appl. WO 2000067024 A1 20001109, 64 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US11990 20000503. PRIORITY: US 1999-305084 19990504.

AB The present invention relates to therapeutic protocols and pharmaceutical compns. designed to treat and prevent cancer. More specifically, the present invention relates to a novel method of treating cancer using antagonists to the endothelin B receptor (ETB) or inactive mimic forms of endothelin-1. The pharmaceutical compns. of the invention are capable of selectively inhibiting the early events assocd. with the development of cancer. The present invention further relates to screening assays to identify compds. which inhibit ETB activation.

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=> s (cancer or neoplasm or melanoma)(l)(treat? or therap?)(l)endothelin?
L93 43 FILE MEDLINE
L94 46 FILE BIOSIS
L95 26 FILE BIOTECHNO
L96 72 FILE CAPLUS
L97 46 FILE EMBASE
L98 2 FILE JICST-EPLUS
L99 96 FILE WPIDS

TOTAL FOR ALL FILES
L100 331 (CANCER OR NEOPLASM OR MELANOMA)(L)(TREAT? OR THERAP?)(L) ENDOTHELIN?

Searched by: Mary Hale 308-4258 CM-1 12D16

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TOTAL FOR ALL FILES
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L115          0 FILE WPIDS

TOTAL FOR ALL FILES
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=> s l100 and "endothelin-1" and endothelin b receptor
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L118          3 FILE BIOSIS
L119          1 FILE BIOTECHNO
L120          2 FILE CAPLUS
L121          1 FILE EMBASE
L122          0 FILE JICST-EPLUS
L123          1 FILE WPIDS

TOTAL FOR ALL FILES
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                E E3+ALL/CT
                E ENDOTHELIN B RECEPTOR/CT 5
                E E4+ALL/CT
                E MELANOMA/CT 5
                E E3+ALL/CT
L1         82455 S E2-E16
                E PROSTATE CANCER/CT 5
                E E3+ALL/CT
                E COLON CANCER/CT 5
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                E OVARIAN CANCER/CT 5
                E E3+ALL/CT
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                E E3+ALL/CT

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Searched by: Mary Hale 308-4258 CM-1 12D16
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L10          23 FILE MEDLINE
L11          19 FILE BIOSIS
L12           4 FILE BIOTECHNO
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L46        1946 FILE CAPLUS
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L48         258 FILE JICST-EPLUS
L49          40 FILE WPIDS
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L52           0 FILE BIOSIS
L53           0 FILE BIOTECHNO
L54           0 FILE CAPLUS
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Searched by: Mary Hale 308-4258 CM-1 12D16

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Searched by: Mary Hale 308-4258 CM-1 12D16

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L123 1 FILE WPIDS
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L127 1 FILE BIOTECHNO
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L129 1 FILE EMBASE
L130 0 FILE JICST-EPLUS
L131 0 FILE WPIDS

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L133 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
2001:59076 Document No.: PREV200100059076. Modulation of human colon tumor-stromal interactions by the endothelin system. Egidy, Giorgia; Juillerat-Jeanneret, Lucienne; Jeannin, Jean-Francois; Korth, Petra; Bosman, Fred T.; Pinet, Florence (1). (1) College de France, INSERM Unit 36, 3 Rue d'Ulm, 75005, Paris: florence.pinet@college-de-france.fr France. American Journal of Pathology, (December, 2000) Vol. 157, No. 6, pp. 1863-1874. print. ISSN: 0002-9440. Language: English. Summary Language: English.

AB Tumor neovascularization is considered to be a critical step in the development of a malignant tumor. **Endothelin** (ET)-1 is a powerful vasoconstrictor and mitogenic peptide that is produced by many **cancer** cell lines. The cellular distribution of the ET components was evaluated in human colon tumors and compared to normal colon. There was more of the ET components (preproET-1, **endothelin**-converting enzyme-1, and ETA and ETB receptors) in adenomas and adenocarcinomas than in the normal colon. There was overproduction of preproET-1 and **endothelin**-converting enzyme-1 in carcinoma cells and stromal vessels, suggesting that they are a local source of ET-1. ETA receptors were present in stromal myofibroblasts of neoplastic tissue, and there were large amounts of ETB receptors in the endothelium and myofibroblasts. There was also a redistribution of alpha-smooth muscle actin-positive cells in the vascular structures of tumors. An experimental rat model of induced colon **cancer treated** for 30 days with bosentan, a mixed antagonist of both ET receptors, confirmed the morphological changes observed during the tumor vascularization. Our data suggest that ET-1 and its receptor play a role in colon **cancer** progression, with ET-1 functioning as a negative modulator of the stromal

Searched by: Mary Hale 308-4258 CM-1 12D16

response.

L133 ANSWER 2 OF 3 MEDLINE DUPLICATE 1
2000511621 Document Number: 20518658. PubMed ID: 11068876. Differential regulation of endothelin secretion and endothelin receptor mRNA levels in JAR, JEG-3, and BeWo choriocarcinoma cell lines and in human trophoblasts, their nonmalignant counterpart. Bilban M; Barth S; Cervar M; Mauschitz R; Schaur R J; Zivkovic F; Desoye G. (Department of Obstetrics and Gynecology, University of Graz, Austria.) ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (2000 Oct 15) 382 (2) 245-52. Journal code: 6SK. ISSN: 0003-9861. Pub. country: United States. Language: English.

AB **Endothelin** (ET) secretion and expression of both ET-A and ET-B receptor subtypes have been found in a number of primary **cancers**. The present study tested (1) whether choriocarcinoma cells and their nonmalignant counterpart, the trophoblast, secrete ET-1 and express ET-A and ET-B receptors; (2) whether ET-1 secretion and receptor mRNA levels are regulated by the same factors in nonvascular tissues as in vascular tissues; and (3) whether such regulation is similar in malignant and nonmalignant cells. All cells secreted ET-1 in similar amounts (approximately 0.8 fmol/10(6) cells per 24 h) and secretion was unaffected by culture and **treatment**. Whereas ET-B accounted for almost all (>98%) ET receptor transcripts in the choriocarcinoma cells, the trophoblasts expressed about 20% ET-A receptor mRNA. During control cultures, ET-B mRNA levels rose in choriocarcinoma, with the greatest relative increase (6-fold; $P < 0.05$ vs 0 h) in BeWo, whereas in trophoblasts, ET-A mRNA transiently changed after 24 and 48 h. **Treatment** with dexamethasone and glucose did not alter the mRNA levels in all cells. Insulin induced changes ($P < 0.05$) in ET-B mRNA levels in BeWo (+90 and +60% after 24 and 48 h, respectively) and JEG-3 (-70%), but not in JAR and trophoblast cells. We conclude that malignant transformation affects the responsiveness of the **endothelin** receptor system to external stimuli and that the regulation of the **endothelin** system differs in vascular and nonvascular tissues.

L133 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
1997:68195 Document No.: PREV199799367398. Methylation of the 5' CpG island of the **endothelin B receptor** gene is common in human prostate cancer. Nelson, Joel B. (1); Lee, Wen-Hsiang; Nguyen, Son N.; Jarrard, David F.; Brooks, James D.; Magnuson, Scott R.; Opgenorth, Terry J.; Nelson, William G.; Bova, G. Steven. (1) James Buchanan Brady Urol. Inst., Dep. Urol., A344, Johns Hopkins Bayview Med. Cent., 4940 Eastern Ave., Baltimore, MD 21224 USA. Cancer Research, (1997) Vol. 57, No. 1, pp. 35-37. ISSN: 0008-5472. Language: English.

AB Production of the potent vasoconstrictor **endothelin-1** (ET-1) by human prostate **cancer** cells accompanies prostate **cancer** progression in vivo. The predominant **endothelin** receptor expressed by normal prostate epithelium, ET-B, is not expressed by any of the established human prostate **cancer** cell lines, and ET-B binding is decreased on prostate **cancer** tissues. ET-B, which may mediate ET-1 clearance and may inhibit ET-1 secretion, is encoded by a gene that contains a 5' CpG island encompassing the transcriptional regulatory region. We examined this regulatory region of the ET-B, receptor gene (EDNRB) to determine whether hypermethylation of cytidine nucleotides accompanies decreased ET-B expression in human prostate **cancer**. We found somatic methylation of CpG island sequences in EDNRB in 5 of 5 human prostate **cancer** cell lines, 15 of 21 primary prostate **cancer** tissues, and 8 of 14 prostate **cancer** metastases (70% of samples overall). Normal tissues contained only unmethylated EDNRB. **Treatment** of human prostatic carcinoma cell line cultures with 5-azacytidine induced ET-B mRNA expression, suggesting that CpG island methylation changes might accompany the apparent transcriptional silencing of EDNRB in vivo.

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